



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 53

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 53

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Advances in

HETEROCYCLIC CHEMISTRY

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ACADEMIC PRESS, INC.

Harcourt Brace Jovanovich, Publishers

San Diego New York Boston

London Sydney Tokyo Toronto

Volume 53

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Academic Press, Inc.

1250 Sixth Avenue, San Diego, California 92101-4311

United Kingdom Edition published by

Academic Press Limited

24-28 Oval Road, London NW1 7DX

Library of Congress Catalog Number: 62-13037

International Standard Book Number: 0-12-020753-2

PRINTED IN THE UNITED STATES OF AMERICA

92 93 94 95 96 97 BC 9 8 7 6 5 4 3 2 1

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Preface

Volume 53 of *Advances in Heterocyclic Chemistry* is an index volume, which includes a cumulative author index, a cumulative title index, and a subject index. These indexes are published only occasionally. The first subject index covered Volumes 1 through 40 and appeared in Volume 40. The second subject index covering Volumes 41 through 45 appeared in Volume 46. In the present volume the subject index covers topics appearing in Volumes 46 through 53. The author and title indexes cover all volumes. It is believed that it is more convenient for users of the series to have to consult only a few subject indexes rather than search through each volume.

In addition to these indexes, Volume 53 contains three regular chapters. Marcial Moreno-Mañas and Roser Pleixats (University of Barcelona, Spain) review dehydroacetic acid, triacetic acid lactone, and related pyrones. They provide the first comprehensive review of this group of compounds, which includes many important natural products.

Valerii Kuzmenko and Alexandr Pozharskii (Rostov-on-Don State University, Russia) give us the first comprehensive coverage of *N*-aminoazoles and bring much needed order into this important field. Much of the earlier literature had assigned structures now known to be incorrect.

Finally, E. S. H. El Ashry, A. Mousaad, and N. Rashed (University of Alexandria, Egypt) cover the chemistry of 2,3,4,-furantriones and their conversion into a very wide variety of bi- and poly-heterocyclic systems.

A. R. KATRITZKY

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Dehydroacetic Acid, Triacetic Acid Lactone, and Related Pyrones

MARCIAL MORENO-MAÑAS AND ROSER PLEIXATS

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Universitat Autònoma de Barcelona
Bellaterra, 08193-Barcelona, Spain*

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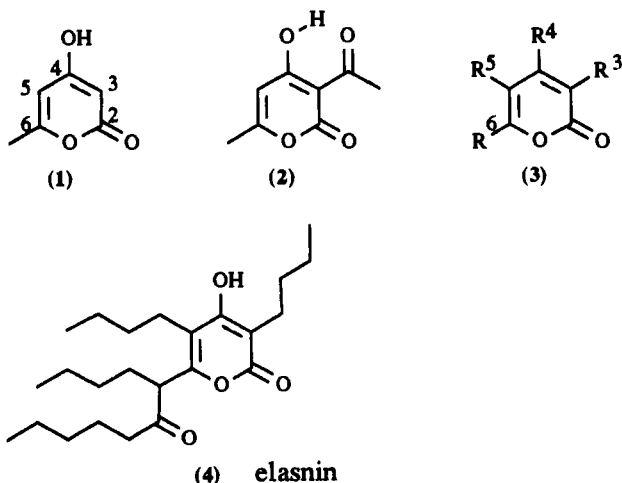
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I. Introduction

4-Hydroxy-6-methyl-2-pyrone (triacetic acid lactone) (**1**) is a natural product of polyketide origin (67JA676, 67JA681). Its 3-acetyl derivative, 3-acetyl-4-hydroxy-6-methyl-2-pyrone (dehydroacetic acid) (**2**), has also been isolated from natural sources (76E1490; 79MI1) and is industrially available by dimerization of diketene. Deacetylation of **2** to **1** was described in the pioneering work by Collie (1891JCS607) and constitutes a good laboratory procedure.

Dehydroacetic acid is mainly used to produce clopidol, a coccidiostatic agent. Small quantities are used as a preservative for fruits and vegetables as well as a stabilizer for plastics. Its sodium salt is also of interest for these applications.

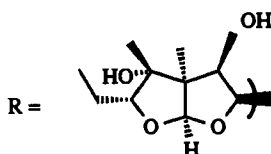
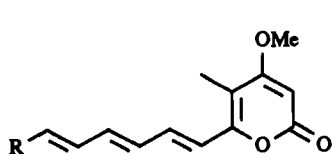
Many natural products containing the basic structure of 4-hydroxy(or methoxy)-6-alkyl-2-pyrone (**3**, $R^4 = \text{OH}$ or OMe) have been isolated, some of them carrying biogenetically plausible groups at C3 or C5 or both.



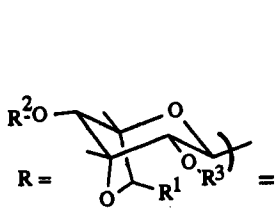
Several natural and synthetic 2-pyrones exhibit remarkable properties that might lead to further developments in the future. Thus, elasinin (**4**), isolated from *Streptomyces* sp., is a specific inhibitor of human leukocyte elastase, an enzyme involved in inflammatory processes such as pulmo-

nary emphysema (78BBR704, 78MI1). Consequently, many more simple pyrones structurally related to elasnin have been synthesized and evaluated as inhibitors of several elastases (84E361; 85JMC1106, 85JMC1828; 87JMC1017; 88MIP1). A family of 4-hydroxycoumarins, benzo derivatives of 4-hydroxypyrones, are anticoagulant agents. Therefore, some 4-hydroxy-2-pyrones have been tested as anticoagulant agents (80AP344; 83AP845, 83AP988, 83AP1030; 84AP262).

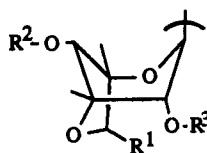
A family of polyketide derived fungal toxins has been identified. They include asteltoxin (5) (86TL2575), aurovertins (6) (86PAC239; 88T6315), citreoviridins (7) [80AG(E)461; 85TL231], citreoviridinol (8) (85TL3243), epiisocitreoviridinol (9) (87CL515), epineocitreoviridinol (10) (85TL6239), isocitreoviridinol (11) (85TL3243), neocitreoviridinol (12) (85TL6239), verrucosidin (13) (86TL723), and normethylverrucosidin (14) (88MI1). They are inhibitors of ATP synthesis and hydrolysis catalyzed by mitochondrial enzymes (86PAC239). In particular, citreoviridin A is related to cardiac beri-beri, an illness associated with yellowish rice in countries of East Asia that have rice-eating populations.



asteltoxin (5)

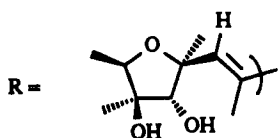


aurovertins



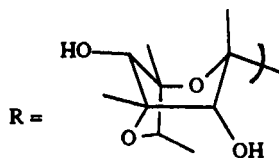
(6)

	R ¹	R ²	R ³
A	Et	Ac	Ac
B	Et	Ac	H
C	Me	Ac	H
D	CHOHMe	Ac	H
E	Et	H	H

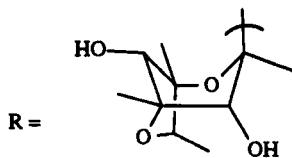


citreoviridins (7)

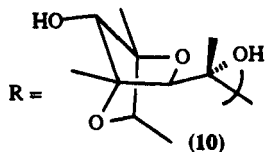
	C3	C5
citreoviridin A	H	Me
citreoviridin C	Me	H
citreoviridin D	Me	Me



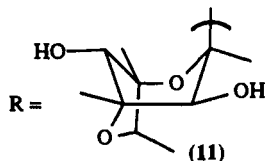
(8)
citreoviridinol



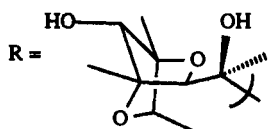
(9)
epiisocitreoviridinol



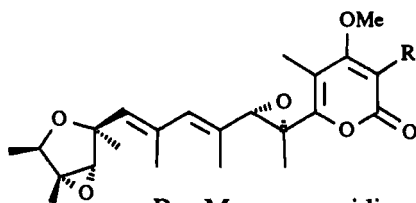
(10)
epineocitreoviridinol



(11)
isocitreoviridinol



neocitreoviridinol (12)



R = Me verrucosidin (13)

R = H normethylverrucosidin (14)

The chemistry of the title compounds has reached maturity. Therefore, we believe that a review on this subject is timely. This review deals with pyrones of general structure **3**, where R^4 is based on an atom more electronegative than carbon, R^3 and R^5 can be any substituent, and R^6 is a noncarboaromatic carbon based radical. Although many pyrones partially saturated at C5—C6 have been described, they are not included here. A review on the natural group of these pyrones has been published (89FOR1). Benzopyrones (coumarins) are also excluded from this work. Bicyclic structures containing a second heterocyclic ring have not been covered in a systematic manner. References up to June 1990 have been covered

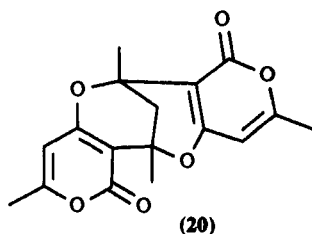
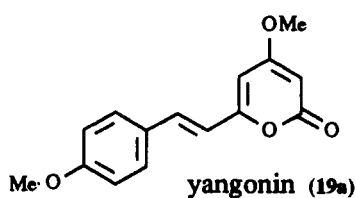
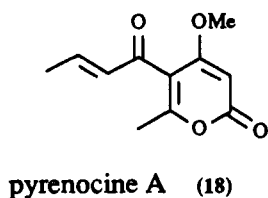
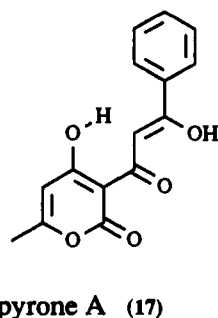
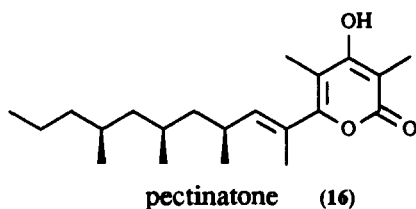
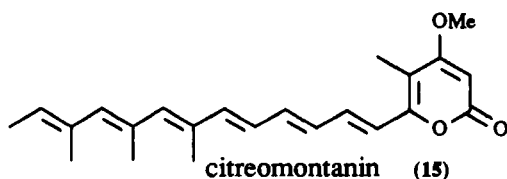
through Chemical Abstracts indices. However, some more recent references directly detected in the original journals are also included.

II. Spectroscopic and Other Physical Data

A. STRUCTURE

1. *Molecular Dimensions: X-Ray Diffraction*

Structural determinations have been performed by X-ray diffraction on natural pyrones asteltoxin (5) (79CC441), citreomontanin (15) [82AX(B)1624], pectinatone (16) (90T1669), pogopyrone A (17)



[86AX(C)1017], pyrenocine A (**18**) (81ABC795), yangonin (**19a**) (71MI1), and on the strained dipyrano-dioxocindione (**20**) (86JHC1511). The carbon-carbon bond distances alternate, pointing out to higher double-bond character at C3—C4 and C5—C6. The ranges are (in pm): O1—C2: 137.5–140.1; C2—C3: 140.7–143.6; C3—C4: 134.6–139.5; C4—C5: 141.9–144.6; C5—C6: 132.8–135.1; C6—O1: 135.3–137.3. There are significant differences between C3—C4 and C5—C6 lengths, the former being larger as required by the conjugation between the OR group at C4 and the carbonyl group at C2. Data on the Schiff base of **2** with aniline are also available [78AX(B)2769].

The cobalt(II) complex of dehydroacetic acid (87MI1), the Ni(II) complex of dehydroacetic acid imine (67AX392), and the Ni(II) and Cu(II) complexes of *N,N'*-bis(dehydroaceto)ethylenediimine (85MI1) have also been studied. In all cases, the most salient feature is the lengthening of the C3—C4 bond, which now ranges between 140.0 and 143.4 pm.

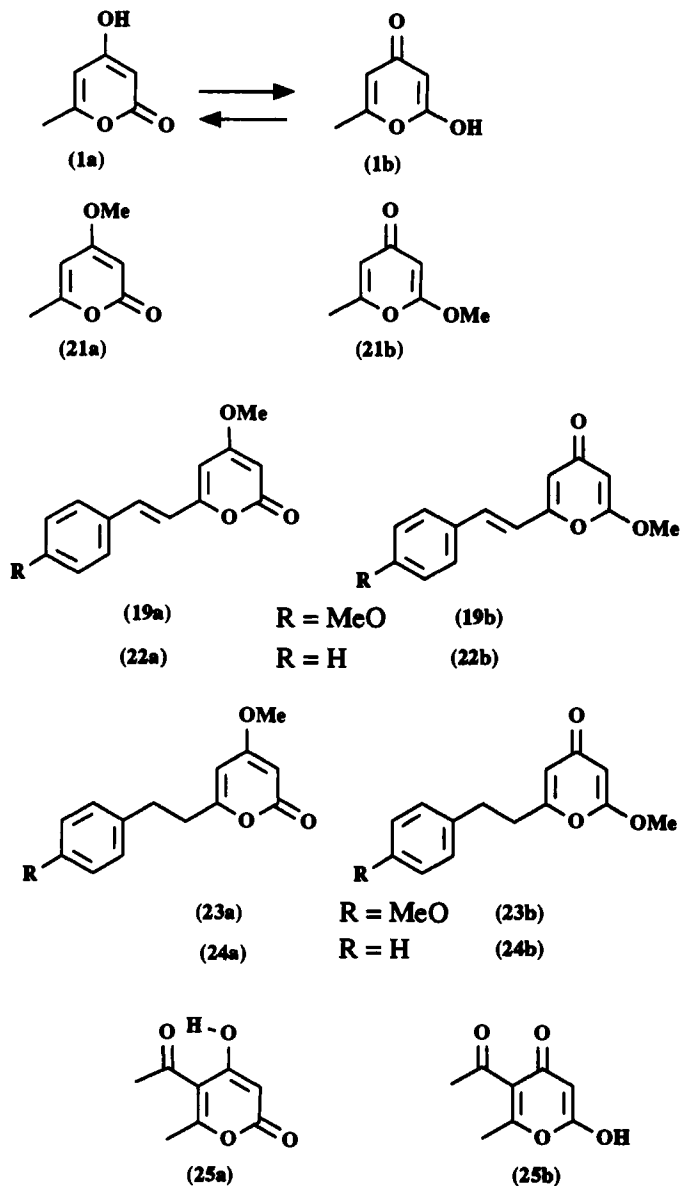
2. UV and IR Spectra

UV spectral data have been instrumental in determining structures of pyrones related to **1**, which can exist in two different tautomeric forms (such as **1a** and **1b**), rapidly interconverting in solution. In general, alkylations of these types of hydroxypyrones occur at C4, but treatment of **1** with diazomethane affords both **21a** and the 2-methoxy-4-pyrone **21b** (60JCS502).

Borsche and co-workers studied the structure of the natural pyrone yangonin (**19a**) by degradation methods (14CB2902), but failed to formulate it correctly. Instead they proposed the alternative 2-methoxy-4-pyrone structure **19b**. However, other authors later suggested the correct structure on the basis of UV and IR data (58T36). They also distinguished between structures **21a** and **21b** for triacetic acid lactone methyl ethers on the same basis. A review on natural 6-styryl-4-hydroxy(and methoxy)-2-pyrones containing a good discussion on structural assignments appeared in 1962 (62FOR131). Further confirmation of structure **19a** for yangonin was obtained by X-ray diffraction (71MI1).

The UV spectra of isomers **21** and related isomeric methyl ethers show differences that distinguish them (62FOR131; 67AP157; 68CJC695; 70T1685; 74CJC825; 79JA4386). Some representative examples are given in Table I.

However, the assignment of structures to **21a** and **21b** relies ultimately on their different reactivity in Diels–Alder reactions: 2-pyrone **21a** acts as a diene, but **21b** does not (60JCS502). The same behavior differences have been observed for related methyl ethers [68AC(R)664].



In general, products with free OH groups at C4 show UV spectra very similar to those of the corresponding 4-methoxy-2-pyrones. Therefore, formulae such as **1a** better represent the structure of triacetic acid lactone and related pyrones in solution.

TABLE I
EXAMPLES OF UV SPECTRA
OF ISOMERIC 2- AND 4-METHOXYPYRONES
IN EtOH

Compound	UV spectra	Reference
1	284(3.89)	63JCS(C)4483
21a	280(3.80)	58T36
19a	360(4.33)	58T36
22a	345(4.32)	58T36
23a	280(4.03)	58T36
24a	280(3.85)	58T36
21b	240(4.12)	58T36
19b	345(3.81)	58T36
22b	330(3.80)	58T36
23b	235(4.22)	58T36
24b	240(4.25)	58T36

IR spectra of 4-hydroxy-2-pyrones unsubstituted at C3 and C5 show a C=O stretching absorption below 1700 cm^{-1} , whereas the corresponding ethers at C4 present this peak above 1700 cm^{-1} . Also, IR spectra are useful to distinguish between ethers at C4 (2-pyrones) and at C2 (4-pyrones). It has been reported that the last absorb at $\sim 1667\text{ cm}^{-1}$ (62FOR131). However, the presence of alkyl groups at C3 (69TL355) and of electron-donating groups conjugated at C6 [66MI1; 67JCS(C)411] might introduce variations.

The 2-hydroxy-4-pyrone structure **25b** was initially assigned to isodehydroacetic acid [63JCS(C)4483]. However, an IR study at high dilution showed a broad absorption ($3200\text{--}3000\text{ cm}^{-1}$) due to intramolecular hydrogen bonding only possible in structure **25a** (87T5245).

3. NMR Spectra

a. *¹H-NMR Spectra.* Examination of a large number of literature ¹H-NMR data shows that protons at C3 absorb at $\delta\ 5.22\text{--}5.60$, and protons at C5 absorb at $5.65\text{--}6.32$. Since both ranges do not overlap, ¹H-NMR spectroscopy offers a safe criterion to distinguish between isomers mono-substituted at C3 or C5 (90T2035).

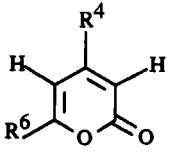
b. *¹³C-NMR Spectra.* Some confusion is evident in papers from the early times of ¹³C-NMR concerning assignment of signals to carbon atoms, mainly C2 and C4. The gated decoupled spectrum of **21a** showed a sharp doublet ($J_{\text{C2-H3}} = 1.6\text{ Hz}$) for the signal at 162.3, which could be assigned to C2. Also single-frequency decoupling experiments permitted assign-

ments of signals at 171.2 and 163.7 to C4 and C6, respectively [81JCS(P1)1173]. The ranges of Table II can be considered safe. Only substituents based on carbon atoms have been included in our selection, which has excluded data for peculiar structures, such as very rigid polycyclic pyrones and pyrones with a high accumulation of polar groups.

Pyrones unsubstituted at C3 and C5 exhibit narrow ranges of chemical shift (δ) values for C2, C3, and C4. As expected, values for C6 are shifted to higher fields by conjugation through R⁶. Both ranges of δ values do not overlap. By contrast, values for C5 are shifted towards lower fields by conjugating substituents R⁶.

Substitution at C3 shifts the absorption of this carbon atom towards lower fields. The extreme value 105.9 corresponds to the CHO substituent (82CJC133). Also, absorptions at C4 are affected. Thus, depending on the absence or the presence of an intramolecular hydrogen bridge between the OH group at C4 and the group R³, two completely different ranges are

TABLE II
RANGES OF δ VALUES FOR ¹³C-NMR SPECTRA OF DIFFERENTLY SUBSTITUTED
4-HYDROXY AND 4-ALKOXY-2-PYRONES

	C2	C3	C4	C5	C6
R ⁶ saturated	162.1–167.7	86.9–90.3	170.9–172.1	99.6–102.5	162.1–166.0
R ⁶ conjugated	162.5–163.8	88.1–93.7	170.2–171.3	100.2–107.4	154.1–158.9

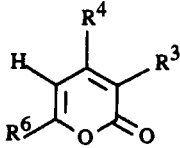
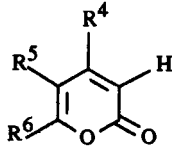
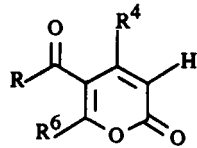
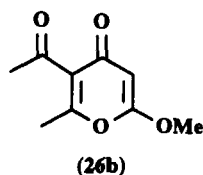
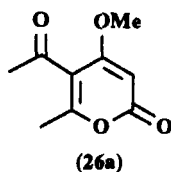
		
C3, 97–105.9 C4, 163.4–166 C4, 180.0–184.9 if intramolecular hydrogen bridge (OH ... X)	C5, 106.1–108.8	C5, 113.7–115.7

TABLE III
 ^{13}C -NMR δ VALUES FOR ISOMERIC 4- AND 2-PYRONES

Compounds	C2	C3	C4	C5	C6	Reference
1a	167.7	89.3	172.1	101.6	163.6	82JCS(P2)513
2	161.2	99.9	181.1	101.4	169.2	82CJC133
21a	162.1	87.3	171.4	100.3	164.6	79CJC1451
	162.3	87.0	171.2	99.9	163.7	81JCS(P1)1173
21b	167.4	89.9	181.7	112.7	161.5	79CJC1451
25	162.5	90.2	169.4	115.4	168.4	87T5245
26a	162.3	87.6	168.4	115.7	163.6	87T5245
26b	167.0	90.1	178.9	125.6	163.4	87T5245



defined. Absorptions for C2, C5, and C6 are not significantly altered by substitution at C3.

Substitution at C5 affects only the C5 δ values, which are shifted to lower fields. Depending on the absence or the presence of a carbonyl group at C1' of the side chain at C5, two different ranges can be identified as indicated in Table II. No noticeable effects appear at C2, C3, C4, or C6 on substitution at C5.

^{13}C -NMR spectroscopy can be used to differentiate 4-alkoxy-2-pyrones from 2-alkoxy-4-pyrones. Some selected examples are included in Table III. The examples show two differences: absorptions for C4 carbon atoms are shifted by 10 ppm or more towards lower fields in 4-pyrones as compared with the isomeric 2-pyrones; and the same effect is observed for C5 (8–17 ppm). Data for **1** and **2** and other 4-hydroxy-2-pyrones are also included for comparison. Further examples of ^{13}C -NMR data for isomeric methyl ethers have been reported (83TL1917, 83TL3055; 87JOC5326).

4. Mass Spectra

The mass spectrum of methyl ether **21a** has been studied in detail (65TL123), and the fragmentation pathways have been confirmed by identi-

fication of metastable ion peaks. Similar fragmentations have been identified for **1** and its isotope isomer dideuterated at C3 and C4—OD positions (65TL123).

Detailed studies on 6-alkyl-4-hydroxy-2-pyrones (71ACS3441) and on **2** (67T2807) have been reported.

Analysis of fragmentations have been very useful in determining structures of several natural and related 2-pyrones, such as luteoreticulin (69TL355), nectriapyrone (75TL1655), secocitreoviridin [82JCR(S)224], citreoviridin [80AG(E)461], and asni-pyrones A and B [89H(28)899] (see Tables IV and V in Section IV for structures). Fragmentation analysis was also used to discover that the methyl group at C-6 of 3,5,6-trimethyl-4-methoxy-2-pyrone was selectively oxidized with selenium dioxide [75S192; 82JCR(S)224].

B. OTHER PHYSICAL DATA

Thermodynamic Data

4-Hydroxy-2-pyrones are acidic compounds. Some pK_a values have been determined in water: **1**, 4.94; **2**, 5.26; **25a**, 3.93 [83JCS(P2)471]. Data for the less acidic Schiff bases of **2** are also available [83JCS(P2)1011].

The enthalpy difference for the equilibrium **21b** \rightleftharpoons **21a** in the gas phase has been measured to be $\Delta H_g = -8.8 \pm 2.1$ Kcal/mol, indicating the higher stability of isomers with the 2-pyrone structure (74JA3867).

III. Preparation from Open Chain Compounds

Preparation of pyrones dealt with in this review can be achieved by modifying previously existing pyrones or by cyclizing open-chain compounds. In this section, we will cover the second strategy, leaving the modification of other pyrones for the reactivity section.

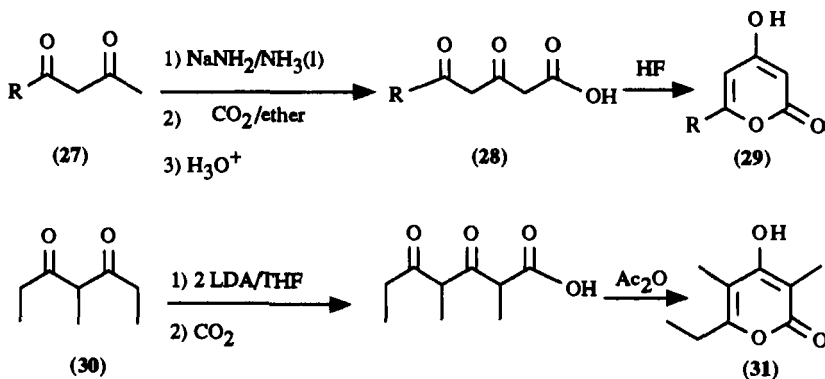
Three main types of preparations from open-chain compounds can be found in the literature. Possibly the largest number of examples involves cyclization of conveniently functionalized open-chain acids or acid derivatives already containing all the final carbon atoms; only the bond O1—C2 is formed in the cyclization. Another series of preparations involves the formation of bonds O1—C2 and C4—C5 at the same synthetic step, starting from precursors containing the fragments C2—C3—C4 and C5—C6—O1. Finally, many examples of preparations are encountered in which bonds O1—C2 and C3—C4 are formed at the same synthetic step. This requires

that the precursors carry the fragments C2—C3 and C4—C5—C6—O1. Some scattered examples outside these three general methods have also been reported.

A. CLOSURE (O1—C2)

The success of this strategy depends on the availability of open-chain materials containing all the carbon atoms possessing the required functionality. Borsche and Bodenstein adopted this type of closure to prepare pyrones of the Kawa family (29CB2515; 62FOR131), but they used open-chain precursors obtained by degradation of the same Kawa pyrones in an attempt to elucidate their structures.

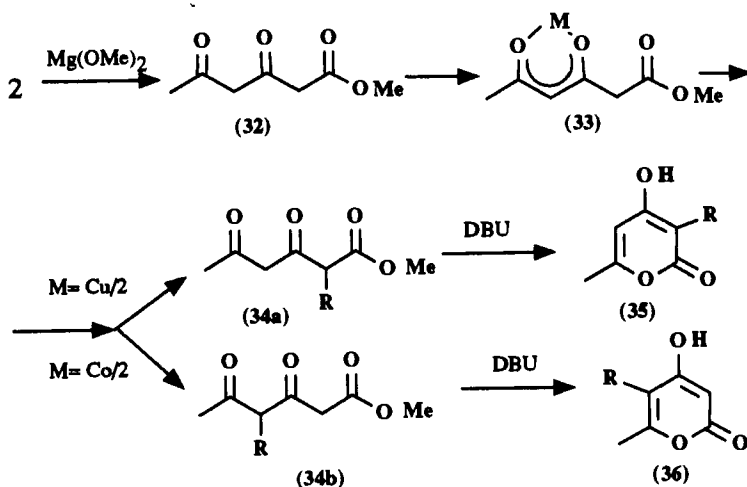
The polyanion chemistry developed by Harris offers an important access to the required open-chain compounds. Thus, treatment of β -diketones **27** with two equivalents of strong base forms the dianions which, by reaction with carbon dioxide (66JOC1032; 68JOC2399, 68T6897; 69T2687; 76JA7733) or with OCS (69T2687; 76JA7733), provides the required β,δ -diketoacids **28**. Cyclization of the diketoacids to 4-hydroxy-2-pyrones **29** is accomplished with HF or acetic anhydride. Triacetic acid lactone labeled with ^{14}C at C2 has been prepared by this method [88JCS(P1)755].



The carboxylation method can be applied to β -diketones substituted at the activated C α , such as **30** [68T6897; 80JCS(P1)2272; 87LA987; 88JA470]. The substituents finally appear at C5 on the pyrone ring (**31**). This has been applied to the synthesis of citreomontanin (**15**) (87TL2455) and asteltoxin (**5**) (84JA4186), in which the substituent is a methyl group and the cyclization steps were performed with trifluoroacetic acid and carbonyldiimidazole, respectively. The reported yields for the carboxyla-

tion reactions and subsequent cyclizations are very variable. However, it has been shown that the success of the carboxylation procedure depends on the amount of ketoenol form in the starting diketone. Thus, yields can be improved by using diketone samples freshly recovered by hydrolysis of their copper(II) complexes (90SC1931). Diketones with bulky substituents at C α that are completely in their diketo forms cannot be carboxylated.

Methyl 3,5-dioxohexanoate (**32**) is easily available from **2** (76SC81). Regioselective alkylations of **32** at its C2 and C4 positions through the Cu(II) and Co(II) complexes **33**, respectively, have been reported. Cyclization of the resultant diketoesters **34a,b** by treatment with diazabicycloundecene (DBU) in benzene gives access to a broad array of 3-alkyl-, 5-alkyl-, and 3,5-dialkyl-4-hydroxy-2-pyrones **35** and **36** (87CC644, 87TL3715; 89TL3105; 90T2035).

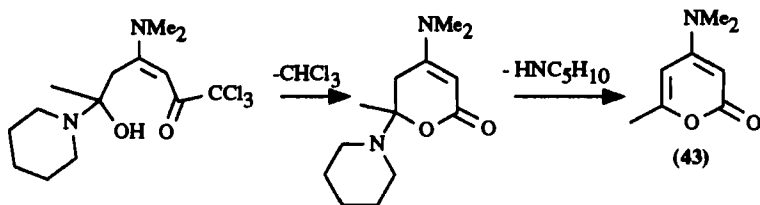
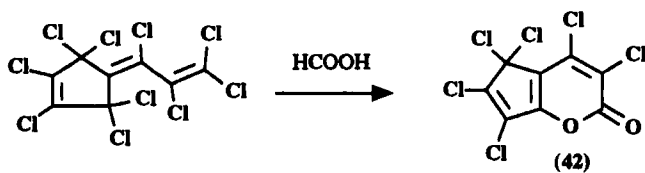
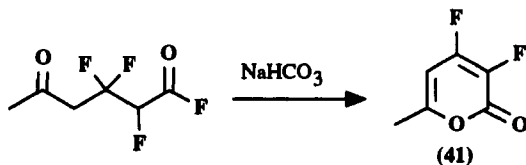
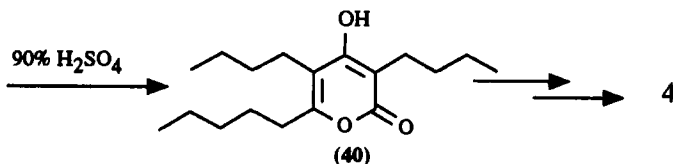
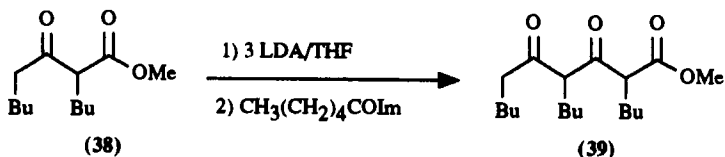
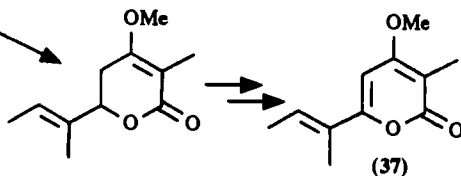


Dianon formation in β -diketoesters instead of β -diketones followed by quenching with electrophiles provides a route to pyrones optionally substituted at C3. Thus, nectriapyrone (**37**) has been obtained in a sequence including oxidation of a C5—C6 dihydropyrone (76TL1903). A similar strategy has been followed in two syntheses of elasnin (**4**) through intermediates **38–40** (80TL1281; 86JOC268) and in the preparation of pyrones related to it (85JMC1828). Further examples can be found (82CJC2821). β,δ -Diketoesters can also be prepared by procedures different from carboxylation, as in a synthesis of luteoreticuln (see Tables IV and V for structure) [76JCS(P1)404] and other pyrones [72JOC1145; 73CC568; 75S259; 77JCR(S)200].

Interesting variations of the O1—C2 closure give rise to pyrones con-

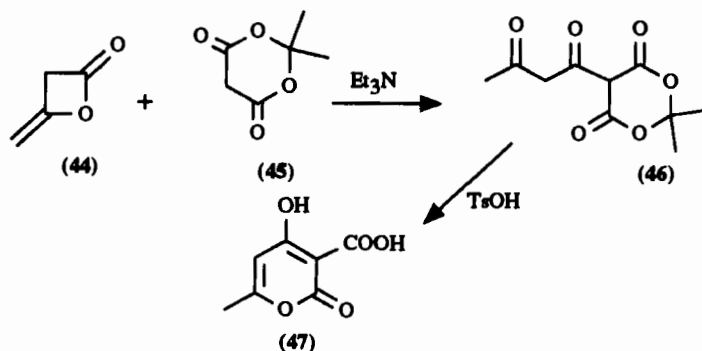


1) 2 base

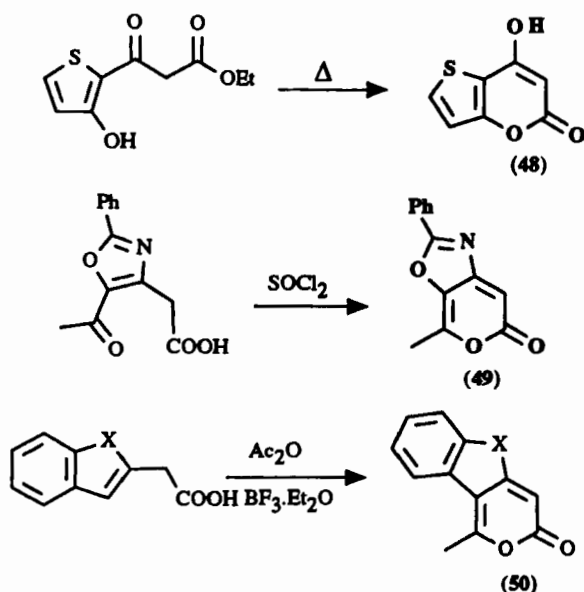
2) $\text{MeCH}=\text{C}(\text{Me})\text{CHO}$ 

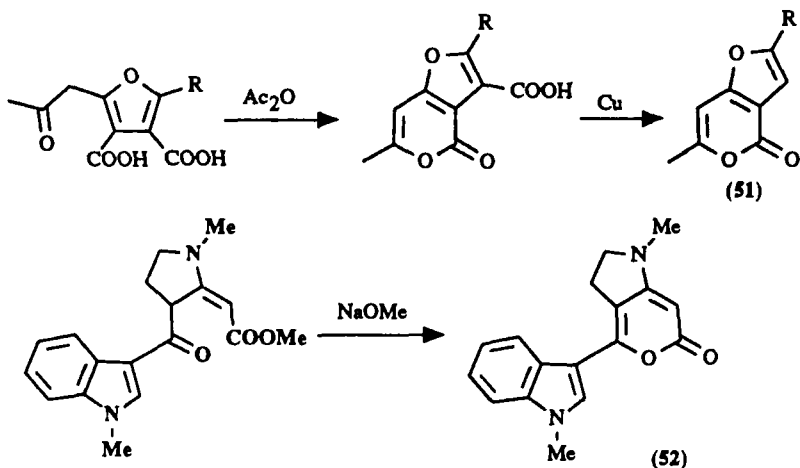
taining fluorine (**41**) (81JOC144), chlorine (**42**) (79BCJ811; 80LA403), and nitrogen (**43**) (85LA149) atoms at C4.

A different approach can be found in the reaction of diketene **44** with Meldrum acid (**45**). Treatment of the resulting derivative **46** with TsOH in benzene forms 3-carboxy-4-hydroxy-6-methyl-2-pyrone (**47**) (84SC265).



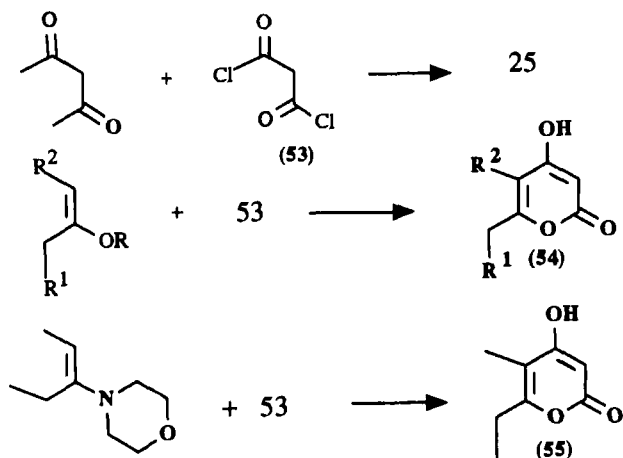
The (O1—C2) closure is also useful for preparing fused pyrones such as **48** (87AP837), **49** (78CJC638), **50** ($\text{X} = \text{NH}$, S) [90JCS(P1)673, 90JCS(P1)681], **51** [78CR(C)381], and **52** [84JCR(S)296.]



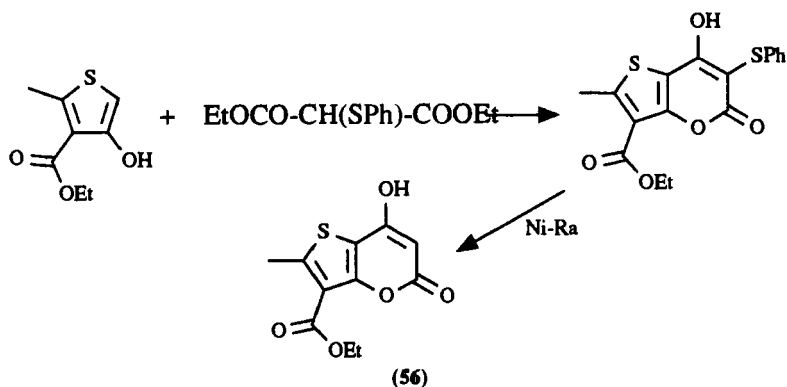


B. CLOSURE (O1—C2) + (C4—C5)

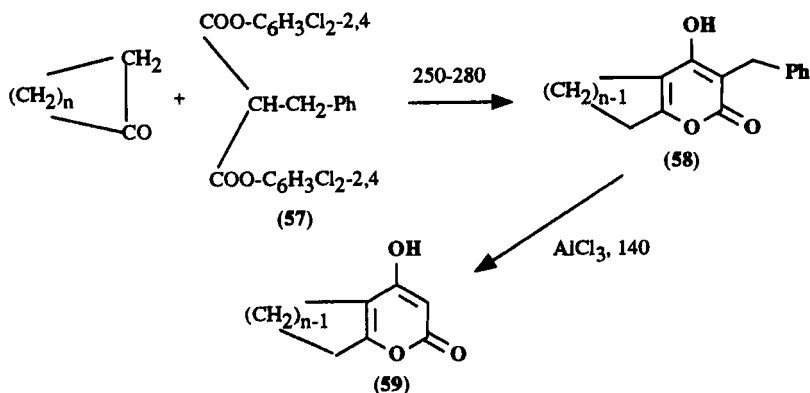
Malonyl dichloride (**53**) is a reagent frequently used to build the C2—C3—C4 part of the required pyrones. The second building block gives the C5—C6 fragment together with substituents at C5 and C6. It can be a symmetrical β -diketone [63JCS(C)4483; 66JA834; 85CJC1161; 87T5245], such as pentane-2,4-dione; isodehydroacetic acid (**25a**) is the final product. Other useful building blocks for preparing pyrones **54** and **55** are enol ethers [82AG(E)871; 84CB3270; 86CB3394], enamines (82P243), and lithium enolates (90CB1175).

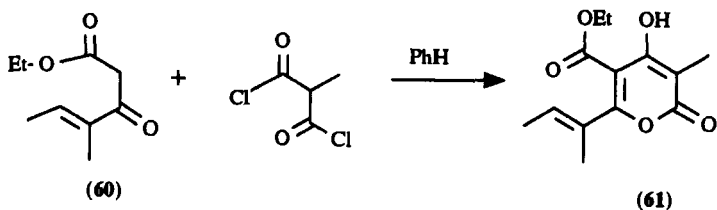


Other activated forms of malonic acid are also useful. Thus, the combinations of carbon suboxide with diketones (68TL3647; 76AP558; 84MI1), ketones (68TL3647), and trimethylsilyl enol ethers [89H(29)913]; of diethyl phenylthiomalonate with a 3-hydroxythiophene derivative (65CR5709) to afford **56**; and of di- and trichlorophenyl malonates with ketones [58M678; 70TL5105; 72JOC1145; 76AP558; 77ZN(B)1189; 79CB2756] and with β -diketones [76AP558; 77ZN(B)1189] have been used to synthesize 4-hydroxy-2-pyrones.



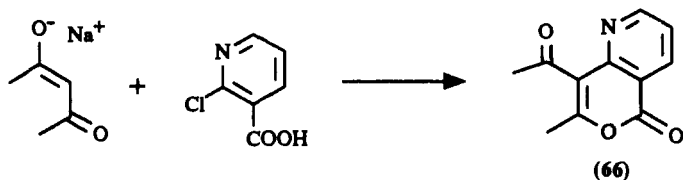
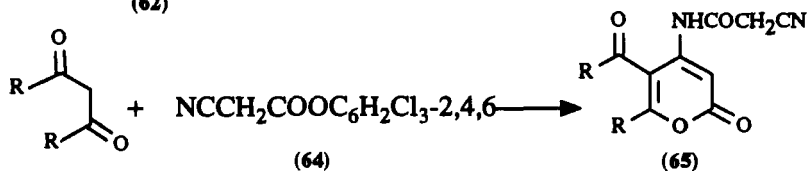
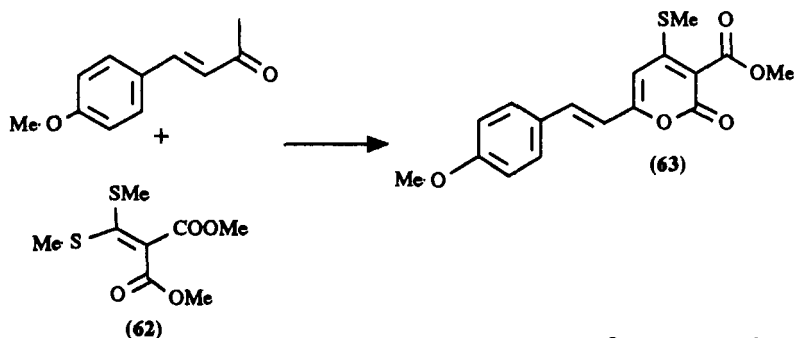
Other substituted malonic esters **57** afford pyrones **58**. The benzyl group at C3 can be eliminated by treatment with aluminium trichloride (58M678). β -Ketoesters such as **60** react regioselectively, with an ester group ending up at C5 of the pyrone ring [66JA834; 69JCS(C)1997; 75S259; 81JHC363], as in **61**. Unsymmetrical β -diketones do not react regioselectively [77ZN(B)1189].





A difficulty encountered in this type of synthesis is the reaction of a second equivalent of **53** at O—C4 and C3 to form a second pyrane ring [68TL3647; 69JCS(C)1997].

Ketene dithioketals **62** are also useful building blocks (84CPB3384; 87JHC1325, 87JHC1557) that give rise to 4-alkylthiopyrones **63**, Cyanoacetic ester **64** reacts with diketones to afford 4-amino-2-pyrone derivatives **65** (76LA250). Also, reaction of 2-chloronicotinic acid with sodium pentane-2,4-dionate gives the pyranopyridine **66** [89IJC(B)173]. These three reactions are remarkable in that they produce 2-pyrones substituted at C4 with atoms different from oxygen.



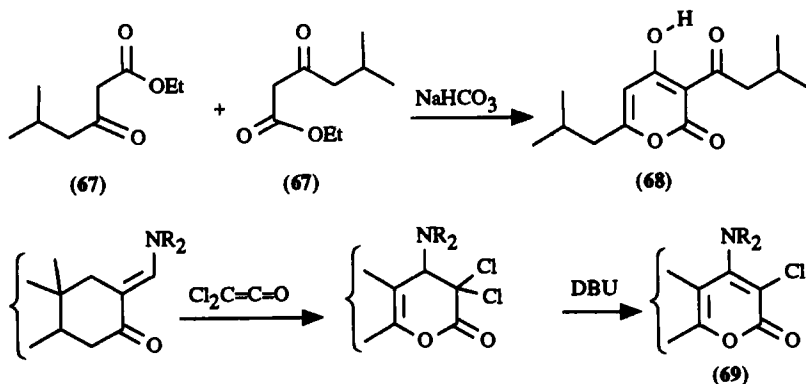
C. CLOSURE (O1—C2) + (C3—C4)

The reaction of two equivalents of β -diketoesters, such as **67**, in the presence of sodium hydrogen carbonate is the old method, leading to 3-acyl-2-pyrones (**68**) [24CB1489; 36CB2373; 55OSC(3)231], which can be frequently found in the chemical literature [33CB1512; 39CB35; 52RTC779; 64RTC39; 65JCS2283; 72JCS(P1)367, 72JCS(P1)692]. Phosphorus pentoxide has also been used as a condensation agent for ethyl 4,4,4-trifluoroacetoacetate in a preparation of 6-trifluoromethyl-4-hydroxy-2-pyrone (82IZV1657).

β -Diketoacids also react in the same manner in the presence of carbonyl-diimidazole (81CPB2762; 87JMC1017).

Since acyl chains at C3 can be efficiently eliminated by treatment with 90% sulfuric acid, this method affords pyrones monosubstituted at C6. Triacetic acid lactone (**1**) is prepared from **2** by this procedure (1891JCS607).

A β -diketoester can be considered a diketene equivalent, and some preparations are based on ketenes and derivatives [70JOC3322; 74BSF(2)2086; 75CJC201; 79LA219; 81JOC147, 81JOC153, 81JOC4047]. Also, thermal treatment of β -diketoesters leads to 3-acylpyrones, possibly through ketenes as intermediates (33CB1512; 39CB35; 71JOC3787).



An exceptional use of a ketene as synthon for pyrones is exemplified by the preparation of steroidal pyrones **69** from dichloroketene (89PHA227).

D. MISCELLANEOUS CLOSURES

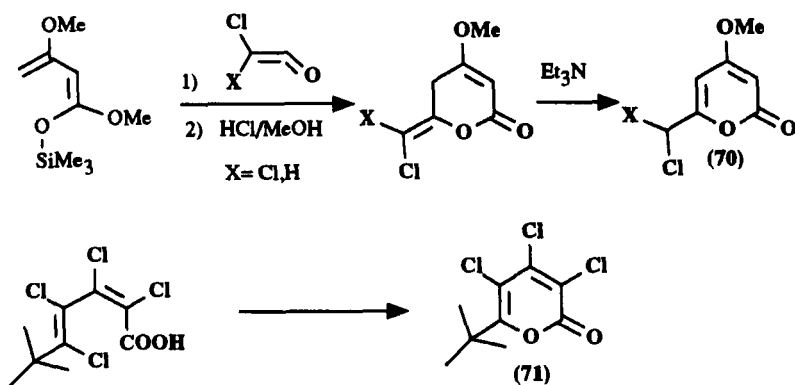
A few examples of pyrone ring formations different from those previously discussed have been reported.

1. (O1—C2) + (C2—C3) Closure

This very infrequent approach has been used to prepare the thienopyrone **48** (67RTC971) from 2-acetyl-3-hydroxythiophene.

2. (O1—C2) + (C5—C6) Closure

Examples can be found in a Reformatsky cyclization combination (81JHC363) and in a hetero Diels–Alder reaction (83JHC501), which gives halogenopyrones **70**.



3. (O1—C6) Closure

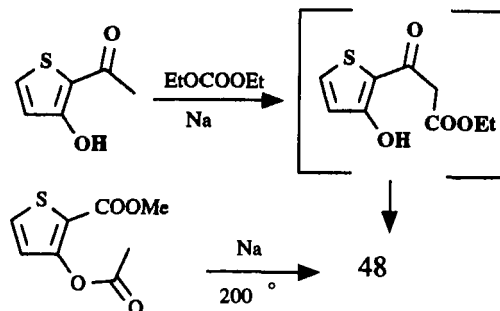
It is noteworthy that this unusual strategy was used in an old synthesis of 5,6-dehydrokawain (50RC144). Much later, a similar approach also based on the displacement of a chlorine atom was described (70CB1011; 80LA403) for the preparation of the polychlorinated pyrone **71**.

4. (C3—C4) Closure

Another preparation of **48** from 3-acetoxy-2-methoxycarbonylthiophene (67RTC971) uses this approach.

E. OTHER PREPARATIONS

The reaction of 3,4,5,6-tetrachloro-2-pyrone with Grignard reagents results in substitution of the chlorine atom at C6 (77CB1000). Nucleophilic



attacks of enolate anions on 4,6-dimethoxy-2-pyrones result in substitutions at C6 (82TL1971; 89TL3505).

Trimerization of ketenes [77HCA3007; 89IJC(B)285] and treatment of acetyl chloride with aluminum trichloride (73USP3743658) produce 4-hydroxy-2-pyrones.

Formation of *N*-substituted 4-amino-2-pyrones has been observed in reactions of ketene with some of its derivatives (64JOC2513).

IV. Natural Occurrence

Many natural 4-hydroxy- and 4-methoxy-2-pyrones have been isolated from natural sources. Some of them bear biogenetically plausible substituents at C3 or C5 or at both, and significant examples were presented in Section I.

Triacetic acid lactone (**1**) is one of the simplest polyketides, and its formation from acetyl-CoA and malonyl-CoA has been proved (68JBC5471). Biogenetic formation of triacetic acid lactone has been considered a derailment from fatty acid biosynthesis promoted by the absence of the reductant NADPH (69MI1). Pyrone **1** has been isolated from microorganisms (67JA676) and is transformed into tropolone derivatives by *Penicillium stipitatum* (67JA681).

6-Acetonil-4-hydroxy-2-pyrone (tetraacetic acid lactone) (**73**) is also a natural product (67JA676).

Curiously, dehydroacetic acid (**2**) has also been isolated from natural sources (76E1490; 78MI1) and should be considered a branched polyketide.

Some families of natural products within the framework of this review should be considered. Thus, the so-called kawa pyrones have attracted considerable attention during the first half of this century. They are com-

pounds possessing the general structures 6-aryl-, 6-(2-arylvinyl)-, and 6-(2-arylethyl)-4-hydroxy(or methoxy)-2-pyrones. Some of them are saturated at C5—C6 of the pyrone ring and are outside the scope of this review. However, a revision on natural C6 substituted 5,6-dihydro-2-pyrones is available (89FOR1). Kawa pyrones are constituents of the kawa resin extracted from the roots of kawa shrubs [*Piper methysticum* FORST (family, piperaceae)]. Kawa resin exhibits stimulating properties which have not been confirmed for the individual components (62FOR131). However, kawa pyrones and other structurally related pyrones are much more broadly distributed in nature, and all of them are listed in Table VI later in this section.

Another interesting group is constituted by fungal toxins such as citreoviridin A (7), asteltoxin (5), aureoverdin B (6), and related pyrones that were discussed in Section I. Studies on their biosynthesis have been performed and, in particular, a review on the biosynthesis of 5–7 has been published (86PAC239).

We present in Table IV the trivial names of all pyrones not categorized as kawa pyrones. Three headings appear in Table IV: (a) Structure, including structural elucidation. References for isolation procedures and natural sources can be found, since they are quoted in the papers dealing with structure elucidations. Therefore, they have been omitted in this review; (b) Synthesis, including only those papers in which the target molecule is accomplished, but omitting reports dealing with syntheses of parts of the molecules. Preliminary communications have not been included when full papers of the same research group have already been published; (c) Biogenetic studies, embracing both biogenesis and biotransformations. Papers included in the useful review of Vlegaar (86PAC239) are not mentioned, except those that were indicated therein to be in press. For these, the full references are now given. We believe this concise presentation includes all the important information required. For structures of the pyrones in Table IV, see Table V.

Table IV embraces a vast array of substituents on the pyrone ring. The occurrence of long chains at C-6 of polyacetate and polypropionate origin is frequent. Structure epimeric at C5' of **109** was tentatively assigned to norpectinatone, a metabolite of the pulmonate *Siphonaria lessoni* (84JOC2506). However, an independent synthesis (86TL4713) showed the synthetic product to be different from norpectinatone isolated from the natural source. The related pectinatone (**16**) has been shown by X-ray diffraction to have the indicated stereochemistry [90T1669, 90JCS(P1)805]. However, the opposite configuration at C5' in the side chain at C6 was also first assigned to **16** (83TL3055). It has been suggested that the stereochemistry of the C6 side chain of norpectinatone (**109**) is as for **16** [90JCS(P1)805].

TABLE IV
NATURAL PRODUCTS

Product	Structure	Synthesis	Biogenetic studies
73 , 6-Acetonyl-4-hydroxy-2-pyrone	67JA676	71T3025 71T3039	67JA676
74 , ACRL toxins of <i>Alternaria citri</i>	86P69		
75 , 3-Acyl-4-hydroxy-2-pyrones	75P2712		
76 , Aglajne-3	87JOC5326		
77 , 6-Alkyl-4-hydroxy-2-pyrones	81MI1		
78 , Arenol	71TL247		
79 , Asnipyrone A	89H(28)899		
80 , Asnipyrone B	89H(28)899		
5 , Asteltoxin	79CC441	84JA4186(+ / -) 90T2353(+)	85CC1633 86PAC239
81 , Aszonapyrone	82ABC1963		
6 , Aurovertins (A,B,C,D,E)	78AX(A)S79 88T6315 ^a	88T6315 ^a	85CC1796 86PAC239
Bisnorhelipyrone (see Colletopyrone)			
15 , Citreomontanin	82AX(B)1624	85TL4789 87TL2455	81P1279
Citreopyrone (See Pyrenocine A)			
7 , Citreoviridins (A,C,D)	77T3077 80AG(E)461 85TL231	85TL231(-) 87JOC5067(+ / -) 88JA470(-)	80AG(E)461 85CC1531 86PAC239
8 , Citreoviridinol	81CL1285 85TL3243	86CL1973	
82 , Coarctatin	75JCS(P1)999		
83 , Colletopyrone	75P1383 76ABC1453		
84 , Conrauanalactone	80P1187		
2 , Dehydroacetic acid	See text		
85 , Deoxyradicinin			88JCS(P1)1283
86 , Deoxyradicinol			88JCS(P1)1283
87 , Dhelwagin	69TL2279		
88 , Diemenensin A	83TL1917		
89 , Diemenensin B	83TL1917		
4 , Elasnin	80JOC3268	80TL1281(+ / -) 86JOC268(+ / -)	80JOC3268
90 , 3-Epideoxyradicinol	84P767	88JCS(P1)1283	
9 , Epiisocitreoviridinol	87CL515	87CL515	
10 , Epineocitreoviridinol	85TL6239		
91 , 6-Ethyl-4-hydroxy-3,5-dimethyl-2-pyrone	89P1546		
92 , Helipyrone	70TL3369 75P1383 80P153 80P639 82P243	70TL5105 82P243	

(continued)

TABLE IV (Continued)

Product	Structure	Synthesis	Biogenetic studies
93, Homoarenol	71TL247		
94, 4-Hydroxy-3,6-Dimethyl-2-pyrone	66JA834	66JA834 75S259	68JA5302
95, Islandic Acid	82CC83		
96, Isoaureothin	61T252	87CL1381	
11, Isocitreoviridinol	85TL3243		
97, 3-Isopentenyl-6-pentadecyl-2-pyrone	82P1393		
98, LL-P880γ	73JOC3542 86ABC1649		
99, Luteoreticulín	69TL355	76JCS(P1)404	
100, Macommelin-9-ol	83CPB3781		88CPB1328
101, Macommelin-8-ol	83CPB3781		88CPB1328
102, Macommelin	83CPB3781		88CPB1328
103, Macommelin-8,9-diol	83CPB3781		88CPB1328
104, Macommelinal	88CPB1328		88CPB1328
105, Macrophin	88CPB1328		88CPB1328
106, Macrohic acid	88CPB1328		88CPB1328
107, Mundulea Lactone	67CC577	67CC577	
37, Nectriapyrone	75TL1655 85P937	76TL1903 81JHC363	
12, Neocitreoviridinol	85TL6239	86CL1973	
108, Norhelipyrone	75P1383		
14, Normethylverrucosidin	88MI1		
109, Norpectinatone	84JOC2506 86TL4713 (See text) 90JCS(P1)805	86TL4713	
110, Obtusifolin	70TL3643		
111, Opuntiol	65T93 73P2059	75S192 82JHC157	
112, P8/1-OG Lactone	81MI2		
113, PC-2	78ABC1625		
16, Pectinatone	90T1669 (See text) 90JCS(P1)805		
114, Phacidin	82CJC2821	82CJC2821	82CJC133
115, Phloraspyron	63ACS1886	63ACS1886	
116–120, Phloroglucinyll pyrones	80P153 80P639 86P1133 89P1613		
121, Phloropyron	61ACS839	61ACS839	
17, Pogopyrone A	84IJC(B)611 86AX(C)1017		

(continued)

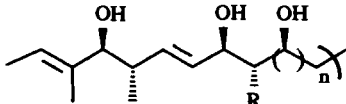
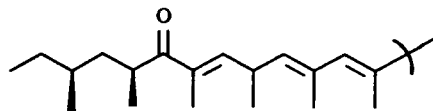
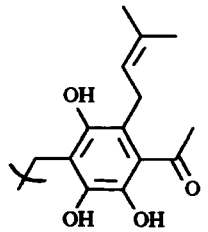
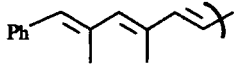
TABLE IV (Continued)

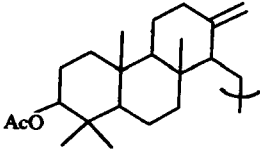
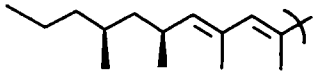
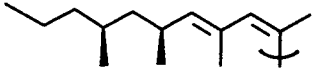
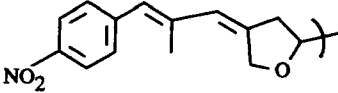
Product	Structure	Synthesis	Biogenetic studies
Pogostone (See Dhelwangan)			
122 , Pycnophorin	86TL2121		
18 , Pyrenocine A or citreopyrone	80TL4481 81ABC795	87T5245	84TL1583 85MI2
123 , Pyrenocine B		87T5245	84TL1583 85MI2
124 , Pyrenocine C	84P2693		85MI2
125 , Pyronylpropionic acid	77BJ715		
126 , Radianthin			88JCS(P1)1283
127 , Radicinin	69JCS(C)1997	69JCS(C)1997 (+/-)	70JA2157
	77TL3271		75ABC915
128 , Radicinol	77TL3271		
129 , Rosellisin	76P1090 83CPB3781		76P1090
130 , Rosellisin aldehyde	76P1090		
131 , Secocitreoviridin	81CL1285	82JCR(S)224	
132 , S39163/F-I	88USP4753959		
133 , Sesquicillin	73GEP2316429		
134 , Solanopyrone A	85TL2453	87TL1175	89CC1282
135 , Solanopyrone B	83TL5373 85TL2453		
136 , Solanopyrone C	83TL5373		
137 , Solanopyrone D	89CC1284		
73 , Tetraacetic acid lactone (See 6-acetonyl-4-hydroxy- 2-pyrone)			
1 , Triacetic acid lactone (See text)			
13 , Verrucosidin	83CC544 84JOC3762 86TL723	88JA5201	

^a Aurovertin B

A family of pyrones with polycyclic substituents at C-6 has been identified (83TL5373; 85TL2453; 89CC1284) and named solanopyrones A, B, C, and D (**134–137**). Solanopyrone C is most unusual in that its substituent at C4 is not found in natural products. Further confirmation of its natural origin would be of interest. Compounds **96** and **99** exhibit a nitro group at a phenyl ring. Other structural types frequently encountered are pyrones with substituted benzyl groups at C3 such as **78**, **110**, **115**, and **116–119**;

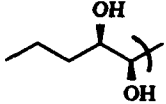
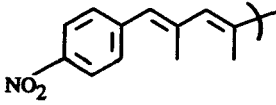

TABLE V
STRUCTURES FOR COMPOUNDS SHOWN IN TABLE IV

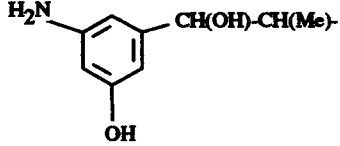
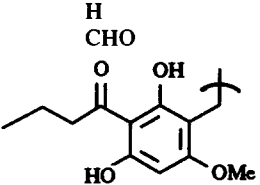
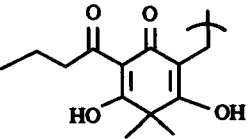
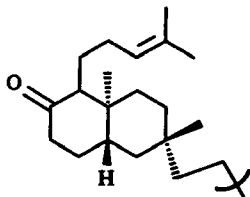
Compound	R ¹	R ⁴	R ⁵	R ⁶
73	H	OH	H	MeCOCH ₂ —
74	H	OH	H	 (R= H, Me) (n= 0, 1, 2)
75	Me ₂ CHCH ₂ CH ₂ CO— and EtCH(Me)CO—	OH	H	Me
76	Me	OH	Me	
77	H	OH	H	C ₂₁ H ₄₃ —, C ₂₃ H ₄₇ —, C ₂₁ H ₄₃ COCH ₂ —, C ₂₃ H ₄₇ COCH ₂ —
78		OH	Me	Me
79	H	OMe	Me	
80	H	OMe	H	as for 79

81		OH	H	Me
82	See formula			
83	See formula			
84	H	OH	H	$n\text{-C}_{15}\text{H}_{31}$
85	See formula			
86	See formula			
87	$\text{Me}_2\text{CHCH}_2\text{CH}_2\text{CO}-$	OH	H	H
88	Me	OH	Me	
89	Me	OH	Me	
90	See formula			
91	Me	OH	Me	Et
92	See formula			
93	As for 78	OH	Me	Et
94	Me	OH	H	Me
95	$\text{MeCH}=\text{CHCH}=\text{CHCOOCH}_2-$	OMe	CH_2OH	$\text{MeOCOCH}=\text{CH}-$
96	Me	OMe	Me	
97	$\text{Me}_2\text{C}=\text{CHCH}_2-$	OH	H	$n\text{-C}_{15}\text{H}_{31}$

(continued)

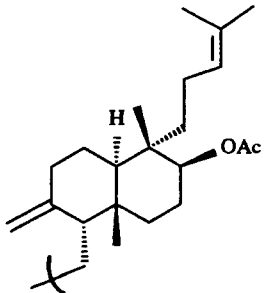
TABLE V (Continued)

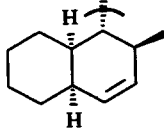
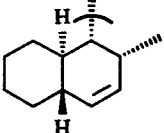
Compound	R ³	R ⁴	R ⁵	R ⁶
98	H	OMe	H	
99	Me	OMe	H	
100	H	OMe	HOCH ₂ CH ₂ —	Me
101	H	OMe	MeCHOH—	Me
102	H	OMe	MeCH ₂ —	Me
103	H	OMe	HOCH ₂ CHOH—	Me
104	H	OMe	HCOCH ₂ —	Me
105	Me ₂ C=CHCOOCH ₂ —	OMe	HOCH ₂ —	MeOCOCH=CH—
106	Me	OMe	Me	HOCOCH=CH—
107	CH ₂ =CHC(Me) ₂ —	OMe	H	PhCH=CH—
108	See formula			
109	Me	OH	Me	
110	See formula			
111	H	OMe	H	HOCH ₂ —

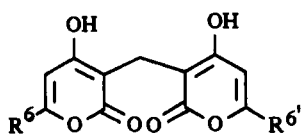
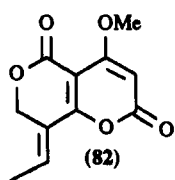
112	Me	OH	H	
113		OMe	H	$n\text{-C}_4\text{H}_9\text{CHOH—}$
114		OMe	H	$n\text{-C}_8\text{H}_{17}\text{CO—}$
115		OH	H	$n\text{-C}_3\text{H}_7\text{—}$
116–120	See formula			
121		OH	H	$n\text{-C}_3\text{H}_7\text{—}$
122		OH	Me	Me
123	H	OMe	$\text{MeCH(OH)CH}_2\text{CO—}$	Me

(continued)

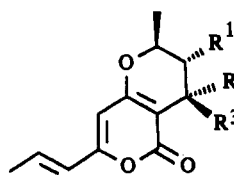
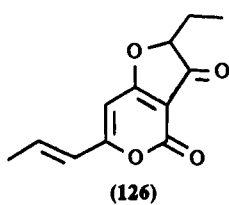
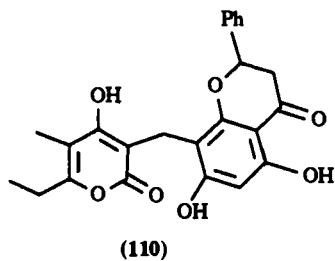
TABLE V (Continued)

Compound	R ³	R ⁴	R ⁵	R ⁶
124	H	OMe	MeCH=CHCH(OH)—	Me
125	H	OH	Me	HOCOCH ₂ CH ₂ —
126	See formula			
127	See formula			
128	See formula			
129	HOCH ₂ —	OMe	HOCH ₂ —	MeOCOCH=CH—
130	HOCH ₂ —	OMe	CHO	MeOCOCH=CH—
131	H	OMe	Me	HCOCH=CH—
132	See formula			
133		OH	Me	Me

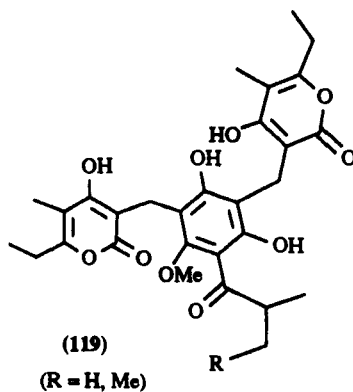
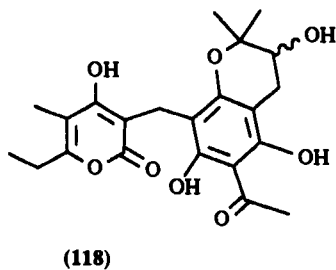
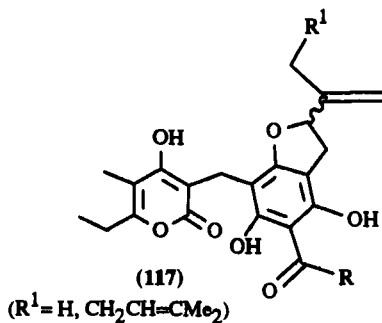
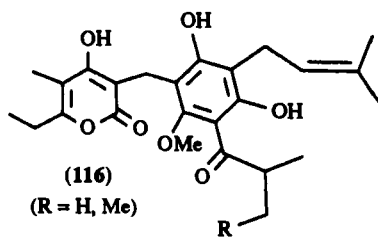
134	CHO	OMe	H	
135	HOCH ₂ —	OMe	H	As for 134
136	HCO	HOCH ₂ CH ₂ NH—	H	As for 134
137	HCO	OMe	H	

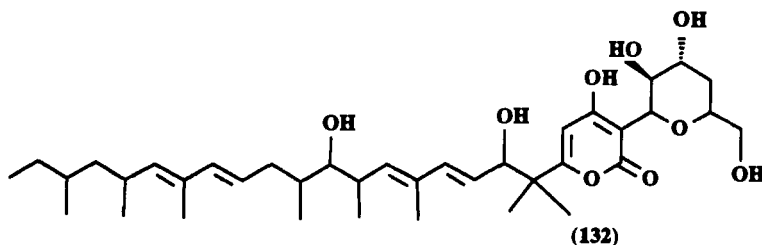
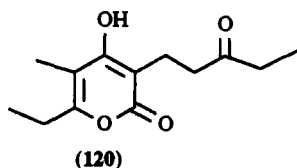


	R^6	R^6
(83)	Me	Me
(92)	Et	Et
(108)	Me	Et



	R^1	R^2	R^3
(85)	H	=O	
(86)	H	H	OH
(90)	H	OH	H
(127)	OH	=O	
(128)	OH	H	OH





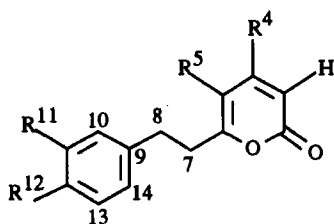
pyranopyrones (82, 85, 86, 90, 127, and 128) and bispyrones (83, 92, and 108).

Kawa pyrones and structurally related pyrones are broadly distributed in nature from a taxonomic point of view. Moreover, their structures are simple. Therefore, we preferred to present in Table VI the names and structures of the known 6-(2-arylvinyl)- and 6-(2-arylethyl)-4-hydroxy(or methoxy)-2-pyrones so far identified. The interested reader can complement the bibliography through conventional methods. We have adopted the numbering which gives numbers 7–14 to the carbon atoms through the styryl (or phenylethyl) group, and when a different numbering has been found (*viz.* 1'–4' for the benzene ring), it has been modified accordingly.

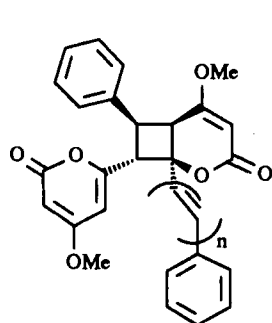
V. Reactivity

The pyrones in this review react at their different ring positions. Position C3 is highly nucleophilic, presenting the characteristic reactivity of enols. Therefore, reactions at C3 result in introduction of an electrophile with conservation of the pyrone structure. On the other hand, positions C2, C4, and C6 are strongly electrophilic. Reactions at C4 produce substitution. However, reactions with nucleophiles at C2 and C6 cause initial opening of the ring, which, in general, is followed by a different cyclization to afford a new heterocyclic system or a substituted benzene. Position C5 is quite inert. The methyl group at C6 can be functionalized in different ways so as to confer electrophilic or nucleophilic reactivity to it.

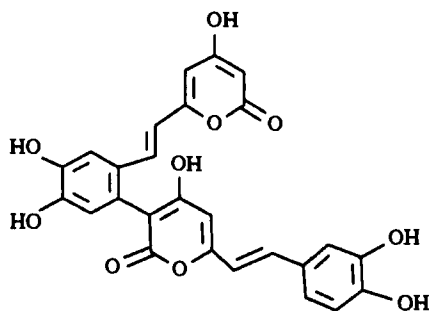
TABLE VI
NATURAL 6-(2-ARYLVINYL)- AND 6-(2-ARYLETHYL)-4-HYDROXY(OR METHOXY)-2-PYRONES



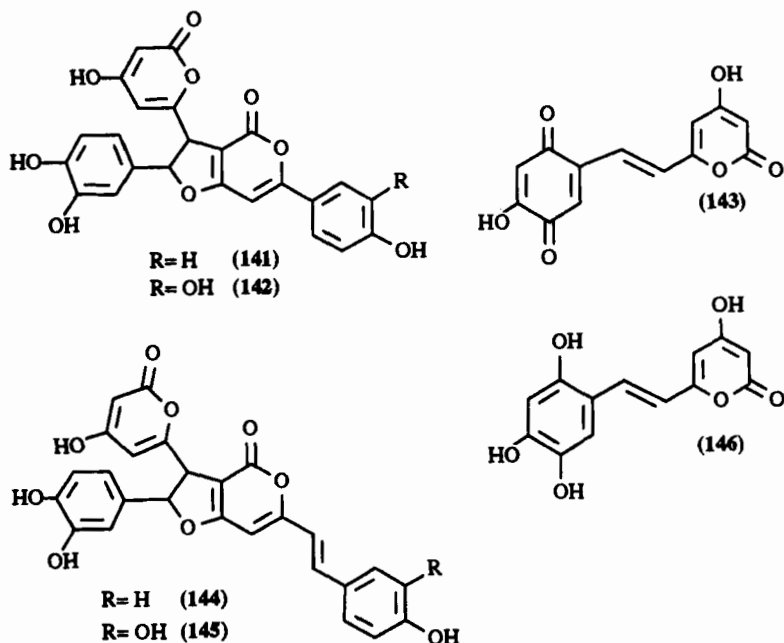
Compound	Structure or synthesis	R ⁴	R ⁵	C7—C8	R ¹¹	R ¹²
Aniba dimer A (138)	77P301			See formulae		
Aniba dimer B (139)	71P3167			See formulae		
Bisnoryangonin	68M11	OH	H	=	H	OH
3,14'-Bihipsidinyl (140)	77CB1058			See formulae		
5,6-Dehydrokawain (22a)	76JOC4070	OMe	H	=	H	H
5,6-Dehydromethysticin	75S192	OMe	H	=	—O—CH ₂ —O—	H
Demethoxyyangonin	85M13	OMe	H	=	H	H
Dihydro-5,6-dehydrokawain (24)	66YZ1184	OMe	H	—	H	H
7,8-Epoxy-5,6-dehydrokawain	86JIC780	OMe	H	Epoxy	H	H
Fasciculine A (141)	77CB1047			See formulae		
Fasciculine B (142)	77CB1047			See formulae		
Hispidin	77CB1058	OH	H	=	OH	OH
12-Hydroxydehydrokawain	77M11	OMe	H	=	H	OH
Hymenoquinone (143)	77CB1063			See formulae		
Hypholomine A (144)	77CB1047			See formulae		
Hypholomine B (145)	77CB1047			See formulae		
Leucohymenoquinone (146)	77CB1063			See formulae		
5-Methoxy-5,6-dehydromethysticin	73CB3119	OMe	OMe	=	—O—CH ₂ —O—	
11-Methoxynoryangonin	85M14	OMe	H	=	OMe	OH
11-Methoxyyangonin	75S192	OMe	H	=	OMe	OMe
Yangonin (19a)	62FOR131	OMe	H	=	H	OMe



n = 1 dimer A (138)
n = 2 dimer B (139)



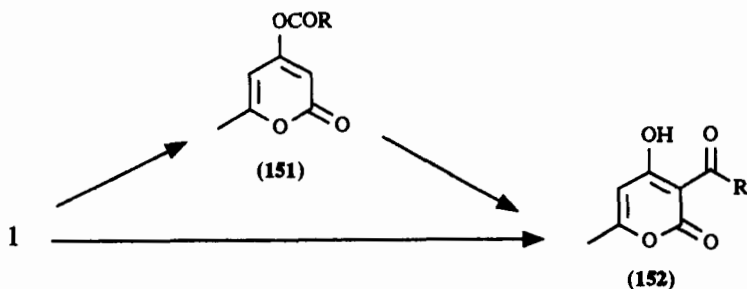
(140)

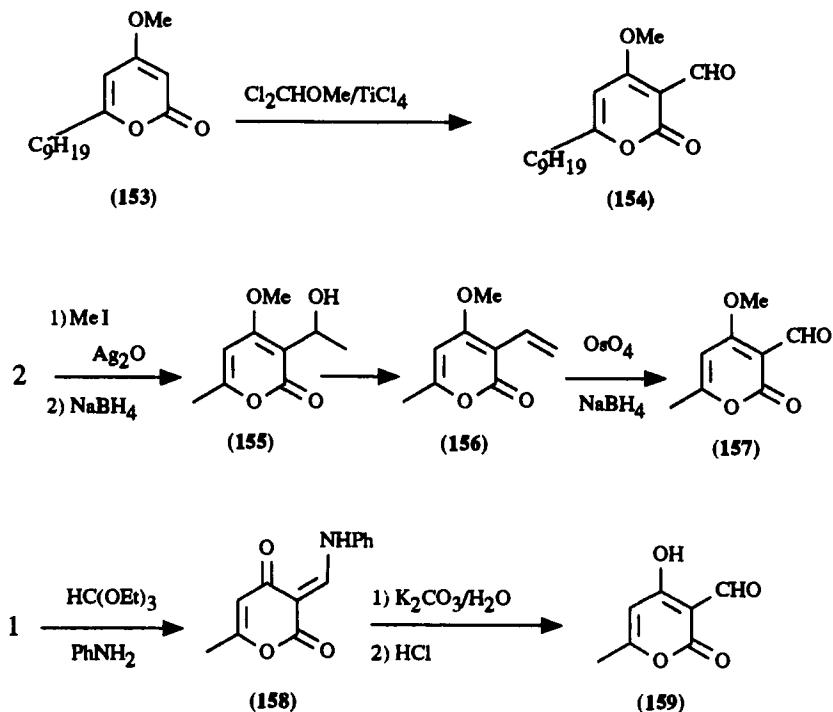


A. REACTIONS THAT MAINTAIN THE 2-PYRONE STRUCTURE

1. Reactions at C3 with Electrophiles

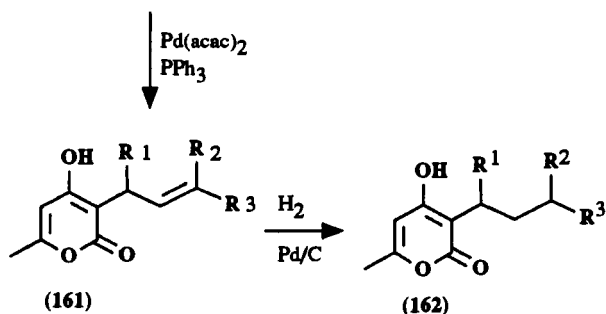
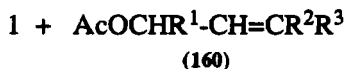
a. *Acylation.* Acylation of **1** and related pyrones gives enol esters **151** under kinetic control, but it gives acyl derivatives **152** under thermodynamic control. Esters **151** can be isolated and further rearranged to **152** (69JHC13). Acylations can be performed with anhydrides or acid chlorides under sulfuric acid (69JHC13) or titanium tetrachloride (77G455) catalysis in refluxing trifluoroacetic acid (69JHC13; 85JMC1106; 87JMC1017; 88MI2) and in hot pyridine (57JPJ94; 88MI2).



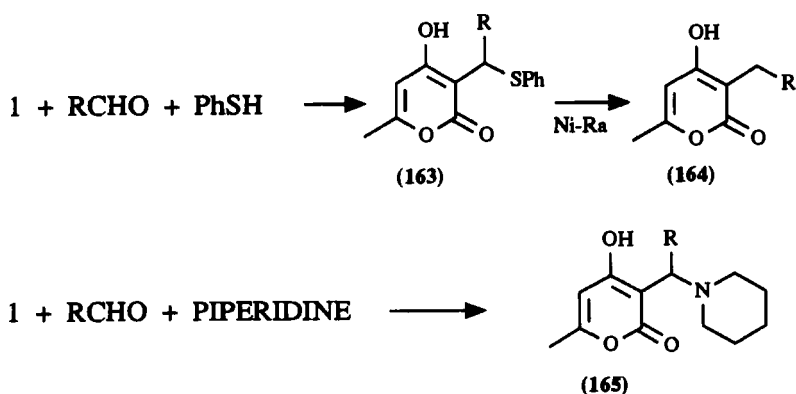


Introduction of a formyl group at C3 on methyl ethers can be performed by direct treatment with dichloromethyl methyl ether under titanium tetrachloride catalysis (82CJC2821), as in the conversion of 153 into 154 or by modification of the side chain of pyrone 2, including an oxidation step on methyl ether 156, to afford 157 (87TL1175). 3-Formyl-4-hydroxy-6-methyl-2-pyrone (159) has been prepared from 1 by reaction with triethyl orthoformate and aniline, followed by hydrolysis of 158 (75M963).

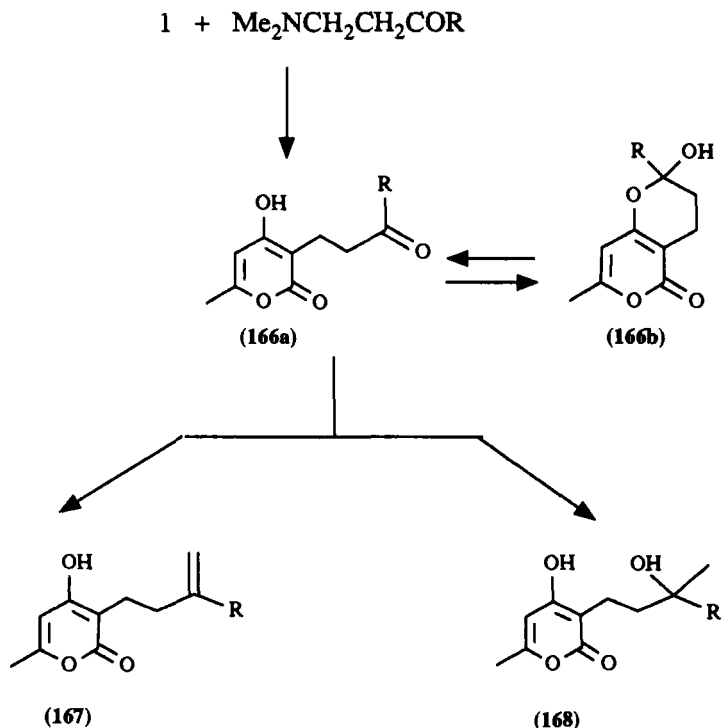
b. *Alkylation.* Compound 1 and related 4-hydroxy-2-pyrones have a high propensity to form enol ethers under conventional alkylation conditions. Therefore, rather specific conditions have to be used to achieve reaction at C-3. This includes reversible reactions that kinetically occur at the oxygen atom. The most general method for alkylation at C-3 is the thermodynamically controlled palladium catalyzed allylation with allylic acetates (160) to afford compounds 161 which, upon hydrogenation, can be easily transformed into 3-alkyl derivatives 162 (88JOC5328). Of course this method permits only the introduction of alkyl groups, both primary and secondary, possessing three or more carbon atoms. Mechanistic stud-



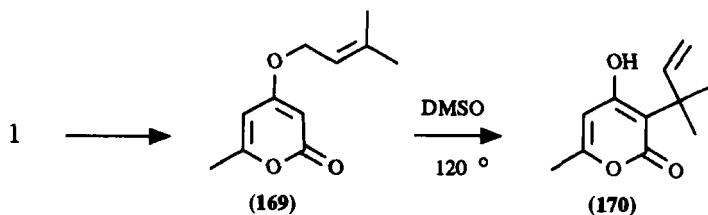
ies on this allylation procedure dealing with stereoselectivity (88JOC5328) and regioselectivity (89TL3109) have been published. The allylation method is complemented by the thioalkylation–desulfuration sequence from **1** to **164** (84S430) that is useful for introducing several benzyl and linear chains as well as the methyl group, depending on the starting aldehyde. Similar reactions using piperidine instead of benzenethiol produce compounds **165** (86JHC413).



The obvious alternative based on the reaction of **1** with alcohols is of limited value and has been applied to alcohols that are precursors of stabilized carbenium ions, both under protic (83AP988) and cobalt(II) chloride catalysis (83MI1) and under purely thermal conditions (59CB982). This last paper describes an unusual case of carbon–carbon formation, although in low yield, under Sandmeyer conditions at C3 of pyrone **1**.



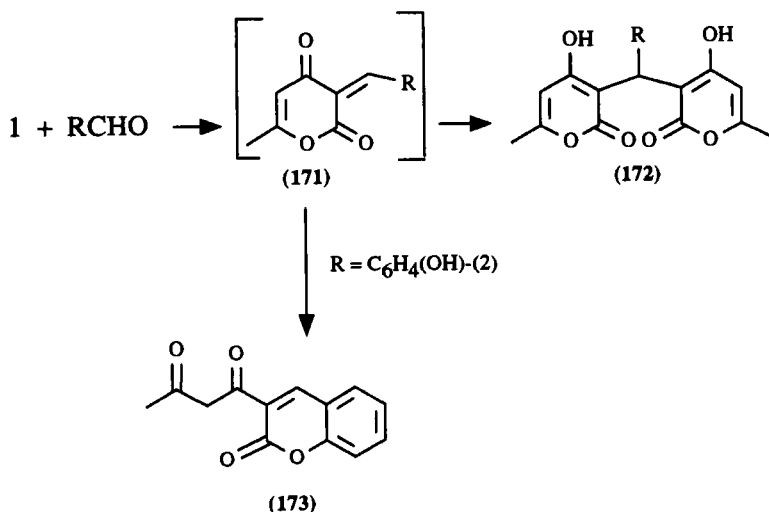
The Michael addition, a reversible reaction, produces alkylation at C3 [83AP988; 86JCR(S)374] as exemplified by the formation of **166**, which can further be elaborated to **167** and **168** [86JCR(S)374]. A preparation of the natural product **94** involves hydrogenation of **158** [82ZN(B)105].



Branched radicals can be introduced at C3 by Claisen rearrangement of enol ethers. This has been used to prepare **170** in one step of the synthesis of Mundulea lactone (**107**) (67CC577). Further examples can be found (88JOC5328).

c. Reactions with Aldehydes and Ketones. Triacetic acid lactone reacts with aromatic (82JHC335; 90T7885) and aliphatic saturated aldehydes

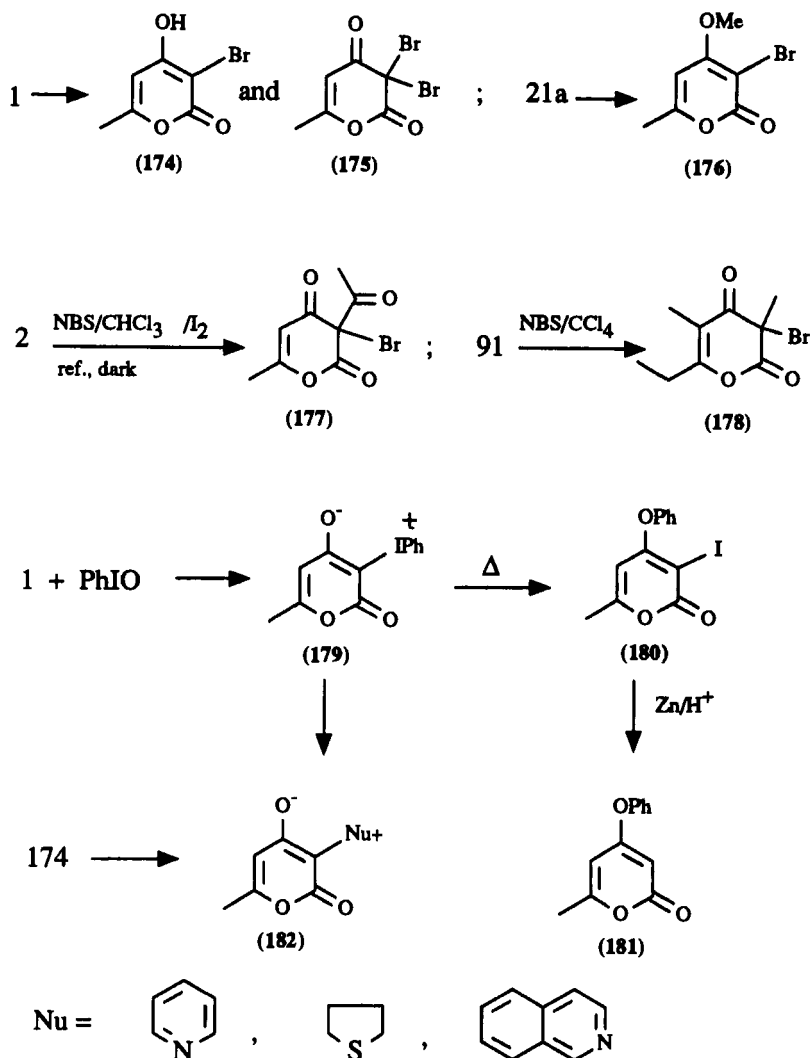
and cinnamaldehyde (84JHC85) to afford compounds of general structure **172**. These reactions seem to take place through the electrophilic intermediate **171** which can be trapped with thiols (82JHC335) and with piperidine (86JHC413) to afford the previously discussed products **163** and **165**. Reactions with 2-butenal (84JHC85) and with ketones (84JHC1369) are rather complicated, and more research is needed before general trends will emerge. Product **20** has been prepared by reaction of **1** with pentane-2,4-dione (84JHC1369).



Reaction of **1** with salicylaldehyde results, instead, in an intramolecular translactonization to afford compound **173** (84JHC1371, 86JHC1511). A similar case has been described in the patent literature (87EGP242805). Great care should be exercised in structural assignment in the pyrone field when translactonizations are possible (87T2381).

The general behavior of 4-hydroxy-2-pyrones towards aldehydes has been used in the synthesis of heliopyrone (**92**) from **55** (70TL5105; 82P243).

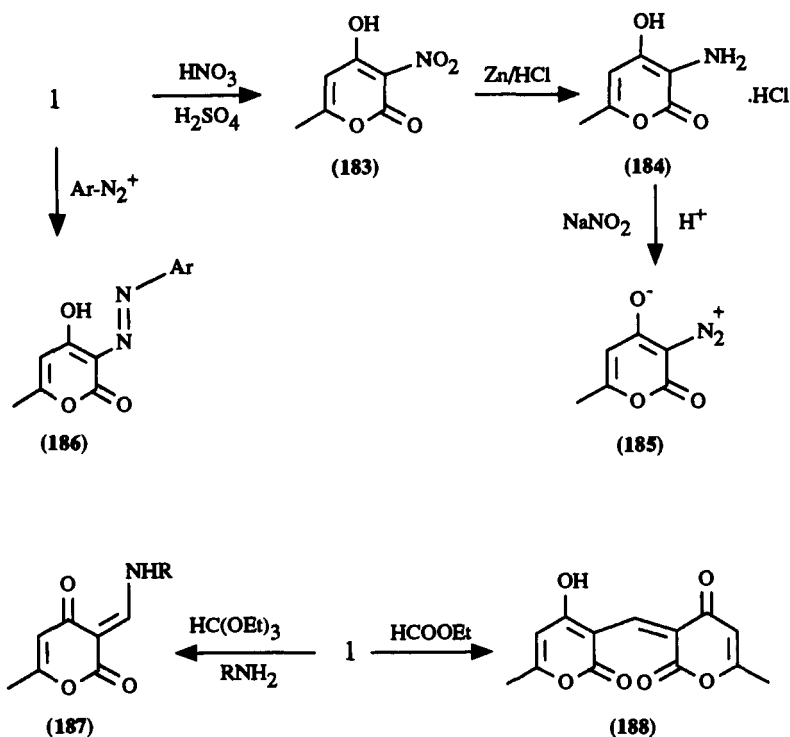
d. *Halogenations*. Two papers deal in great detail with brominations of pyrones covered in this review (70JOC1329; 85JHC1537). Whatever the reagent (bromine or NBS) or the conditions, 4-hydroxy-2-pyrones are always brominated at C3, as exemplified by the formation of **174** and **175** (51CB343; 70JOC1329; 85JHC1537). However, the methyl ether **21a** can be brominated at C3 under an ionic mechanisms to form **176** and at the methyl group at C6 under radical conditions (74JOC3615; 85JHC1537) using *N*-bromosuccinimide (NBS) and a radical initiator. The high ten-



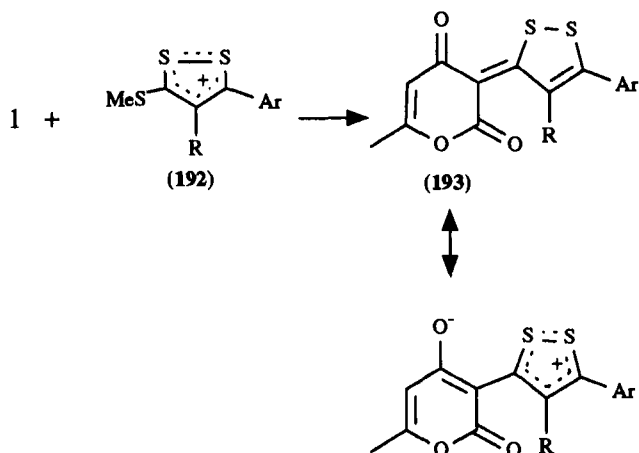
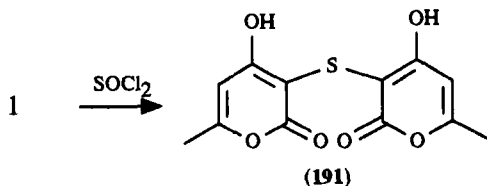
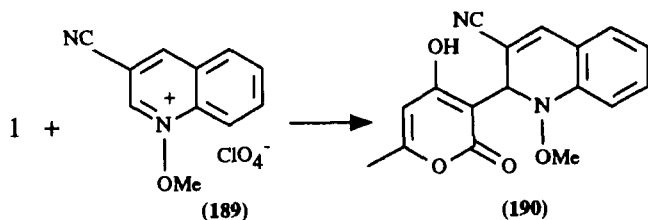
dency of 4-hydroxy-2-pyrones to be brominated at C3 is evident in the transformations of **2** into **177** (70JOC1329) and of **91** into **178** (87LA987).

Reaction of **1** with iodosobenzene affords the betaine **179**, which thermally rearranges to the iodo derivative **180**, which can be reduced to **181** [83ZN(B)398]. Reactions of **179** and **174** with neutral nucleophiles afford the betaines **182** [83ZN(B)398].

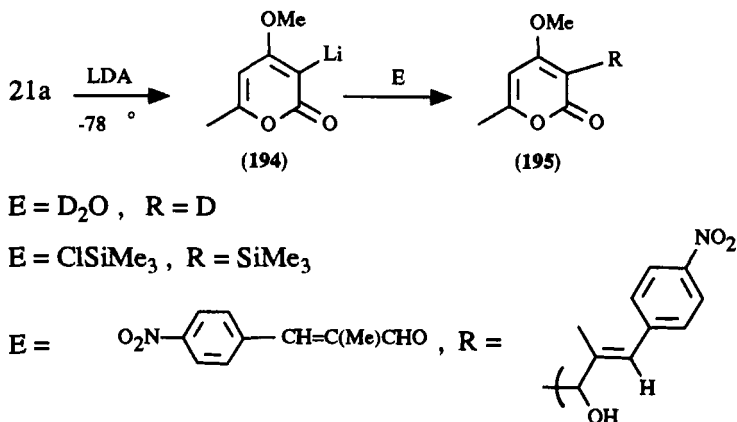
e. *Other reactions.* The sequence starting from **1** and leading to 3-nitro (**183**), 3-amino (**184**), and 3-diazo (**185**) compounds has been reported (51CB343; 89MI1). Diazotization of **1** produces compounds **186** (88MI3) and has attracted a great deal of attention in the patent literature (i.e., 78GP2808795) since the resulting diazo compounds can be converted into *N*-arylpyridazines (see Section V,B,2), which have potential application as agrochemicals. Compounds **187** can be prepared by reaction of **1** with triethyl orthoformate and amines [75M963; 82ZN(B)105; 84M1353; 87ABC2775; 88MI3]; an application was discussed in Section V,A,1,b. If no amines are present, **1** reacts with ethyl orthoformate to give a 2:1 adduct to which structure **188** has been assigned [76ZN(B)95].



Pyrone **1** reacts with pyridinium salts such as **189** to afford **190** (88AP897). It also reacts with other related salts (85T4529) and *N*-acylimines (88T5403). Treatment of **1** with thionyl chloride affords the sulfide **191** (82MI1). Reactions of **1** with 5-aryl-1,2-dithiolylum iodides (**192**) give betaines **193** (77T869). One case of sulfonyloxylation of **1** has been described (90JOC315).

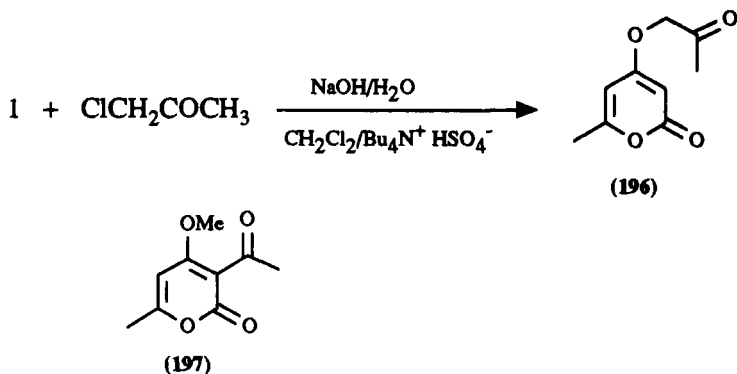


Treatment of **21a** with lithium diisopropylamide (LDA), or with *n*-BuLi in tetrahydrofuran (THF) at -78°C followed by quenching with electrophiles has been reported to afford products **195** through the kinetically controlled lithium derivative **194** (80CC1227). This behavior is rather exceptional since **21a** reacts at the methyl group at C6 (See Section V,A,4,b) in the presence of magnesium methoxide in refluxing methanol. Also, pyrones substituted at C5 with methyl or methoxycarbonyl groups react at the same methyl group at C6 under lithiation conditions that can be considered identical to those described here to yield **194**. However, another paper describing lithiation and quenching of the lithium derivative of **21a** at C3 with an aldehyde has appeared [91JHC(ip)].



2. Reactions at C4

a. *Formation of Ethers and Esters.* We have already discussed in Section II,A,2 the reaction of **1** and related pyrones with diazomethane, which results in mixtures of 4-methoxy-2-pyrones and their isomeric 2-methoxy-4-pyrones. However, reactions with methyl sulfate in either refluxing acetone or butanone in the presence of potassium carbonate is the commonplace method widely used to prepare 4-methoxy-2-pyrones (see, for instance, 60JCS502). Other ethers are much less frequent and can be prepared with alkyl halides/KOH/dimethyl sulfoxide (DMSO) (86MI1) and with ROH/diethyl azodicarboxylate/triphenylphosphine [79JCR(S)110]. A special case is ether **196**, which can be prepared from chloroacetone under carefully controlled phase transfer conditions (83CB3366). Special comments apply to methyl ethers **26a** from isodehydroacetic acid and to **197** from dehydroacetic acid, which can be better



prepared by reacting the corresponding hydroxy compounds with iodo-methane/silver oxide (81TL4005; 87TL1175).

Demethylation of methyl ethers to recover the OH group at C4 has been said to occur with trimethylsilyl iodide in chloroform (82TL1971).

The pronounced tendency of 4-hydroxy-2-pyrones to form enol ethers is the reason for the difficulties encountered on alkylation of position C3, as already discussed.

Esters at C4 are formed as intermediates in acylations at C3 (69JHC13), although they can be isolated (see Section V,A,1,a). Special esters are the methanesulfonates (85JHC433) and the 4-toluenesulfonates (71T1043; 85S699). Hydrolysis of an acetate has also been described (85JMC1828).

b. *Reactions at C4 with Nucleophiles.* These reactions are a source of 2-pyrones possessing heteroatoms at C4 different from oxygen. The other way to access such compounds is the direct preparation from open-chain compounds; this was discussed in Section III.

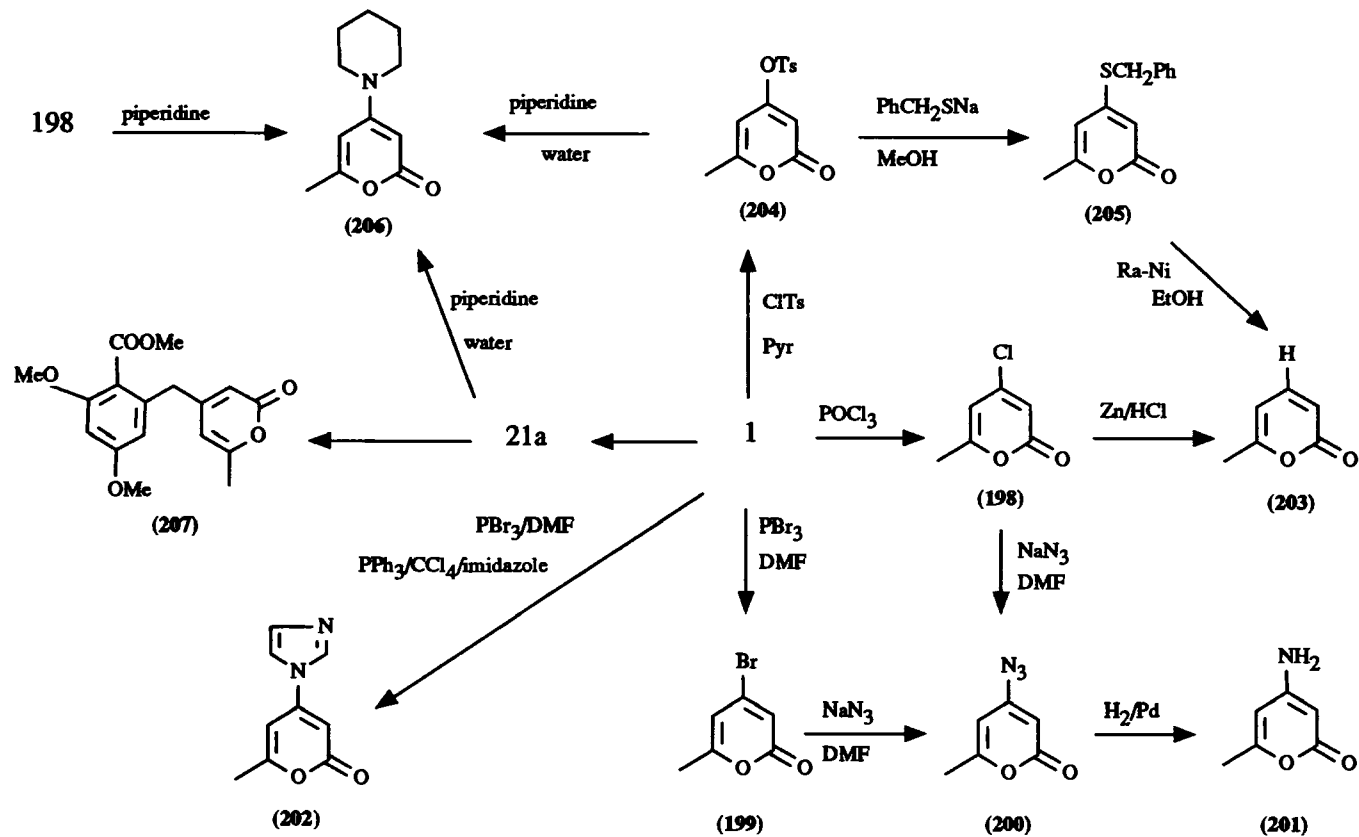
Pyrone **1** can be converted into the chloro and bromo derivatives **198** (64RTC39) and **199** (90T7885). Both compounds have been transformed into the azide **200**, which, on hydrogenation, affords 4-amino-6-methyl-2-pyrone (**201**) (90T7885). The imidazole derivative **202** is also obtained in a single synthetic step from **1** (90T7885).

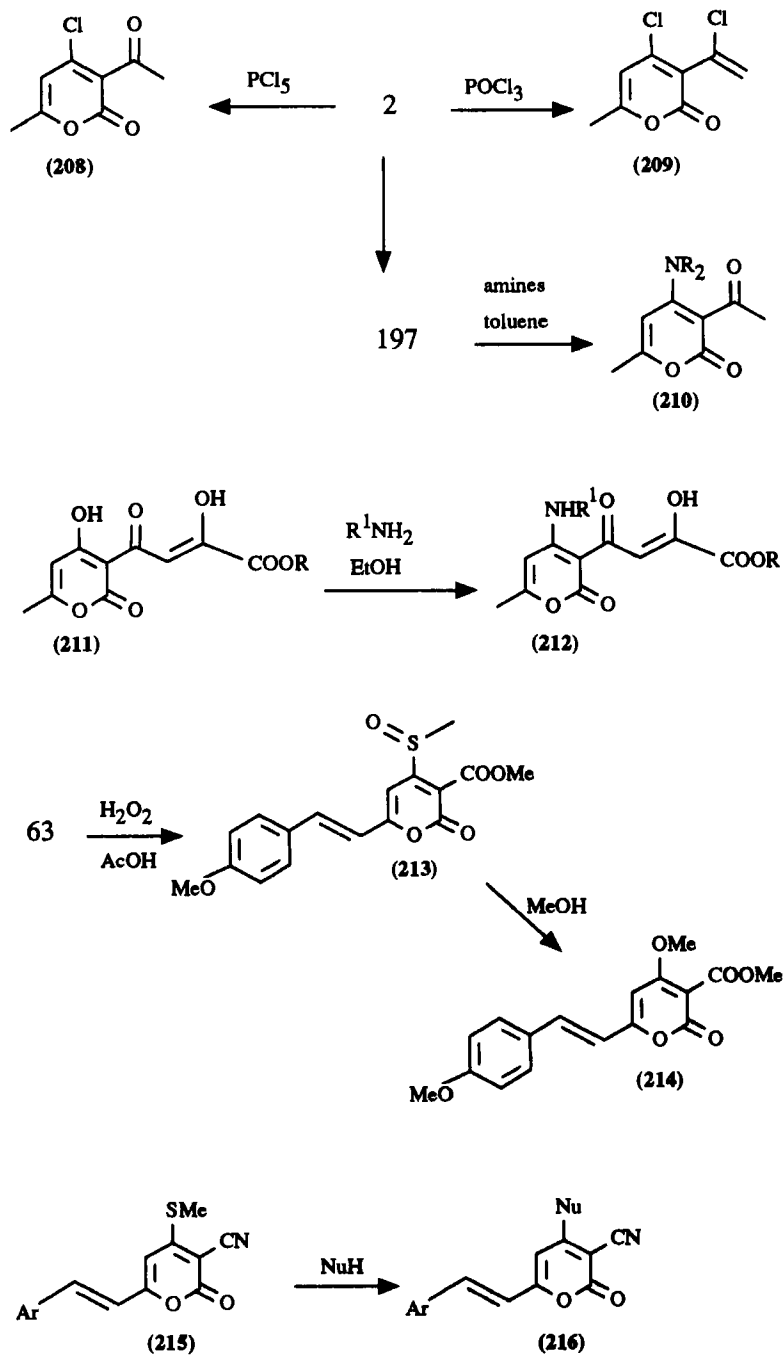
Reduction of **198** gives rise to the C4 unsubstituted pyrone **203** (64RTC39), which is also accessible by conversion of the 4-toluenesulfonate **204** into the sulfide **205** and further hydrogenolysis (71T1043). It has also been reported that the 4-methoxy group of **21a** can be a reasonable leaving group, as shown by its substitution by piperidine to afford **206** (76MI1). This aminopyrone can also be prepared from both **198** and **204** (76MI1). A carbon nucleophile has also been used for 4-methoxy group substitution, as in the preparation of **207** [84JCS(P1)1053].

Dehydroacetic acid (**2**) can also be converted into the monochloride **208** [82IJC(B)372] and the dichloride **209** (87BCJ4425). The chain at C3 of pyrone **209** can be converted into an ethynyl group (88MI4).

Direct replacement on the methyl ether **197** by ammonia and primary amines (72IZV917) and by secondary amines (73IZV1122, 73T1083) to yield aminopyrones **210** has also been reported. It seems that the presence of a carbonyl group directly linked at C3 facilitates displacement of oxygen-based leaving groups, as shown by the conversion of **211** into **212** (83MI2).

Further examples of displacements occur on sulfides **63** and **215** prepared from open-chain compounds (see Section III,B). Enhancement of the leaving group ability of the methylthiolate anion can be achieved



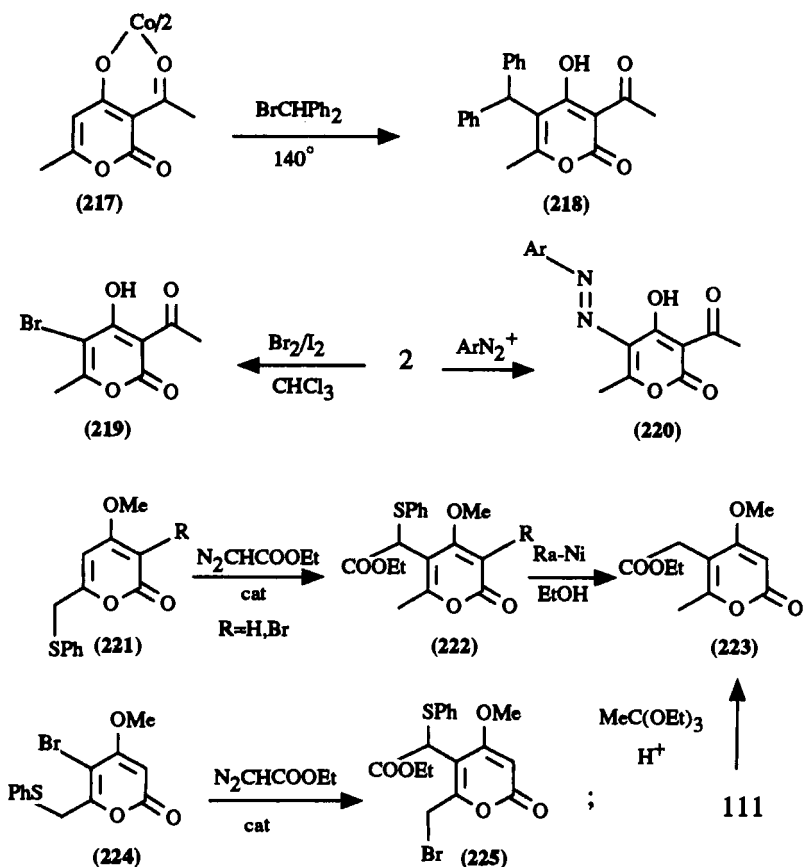


by conversion into the corresponding sulfoxide (**213**) from which **214** is obtained (87JHC1557).

Amines, malonates, and methanol are useful nucleophiles in the formation of pyrones **216** (75CPB2390; 84CPB3384).

3. Reactions at C5

Position C5 is not sufficiently activated towards attack by electrophiles, and very few reactions have been reported. Thus, the reaction of the cobalt(II) complex of dehydroacetic acid (**217**) with benzhydryl bromide gives pyrone **218**, although in modest yields and accompanied by many other products. This reaction is exceptional rather than general, and it seems to involve free radicals (81CL173; 83M11). Harris described bromi-



nation of **2** at C5 to afford bromopyrone **219** in a reaction that probably goes through addition of bromine to the double bond C5—C6 followed by hydrogen bromide elimination (70JOC1329). This useful reaction has permitted the preparation of a vast array of pyrones brominated at C5 with different functionalizations in the rest of the molecule by transformations starting from **219** (85JHC1537). In view of the inertness of C5 towards electrophiles, it is surprising that pyrone **2** reacts with diazonium cations to afford diazocompounds **220** (66JIC377).

An indirect method of alkylating position C5 is by [2,3]sigmatropic rearrangements of sulfonium ylides, as exemplified by the reaction of **221** with ethyl diazoacetate under $\text{Cu}(\text{acac})_2$ or $\text{Rh}_2(\text{OAc})_4$ catalysis. The intermediate sulfonium ylide rearranges to **222**, which is desulfurized with Raney–nickel to **223** (87CB1413). A similar sequence using dimethyl diazo-malonate has also been described in the same paper. A different preparation of **223** has been achieved by treatment of opuntiol (**111**) with triethyl orthoacetate under acid catalysis (82JHC157) in a reaction that takes place by a Claisen rearrangement of an intermediate allyl vinyl ether.

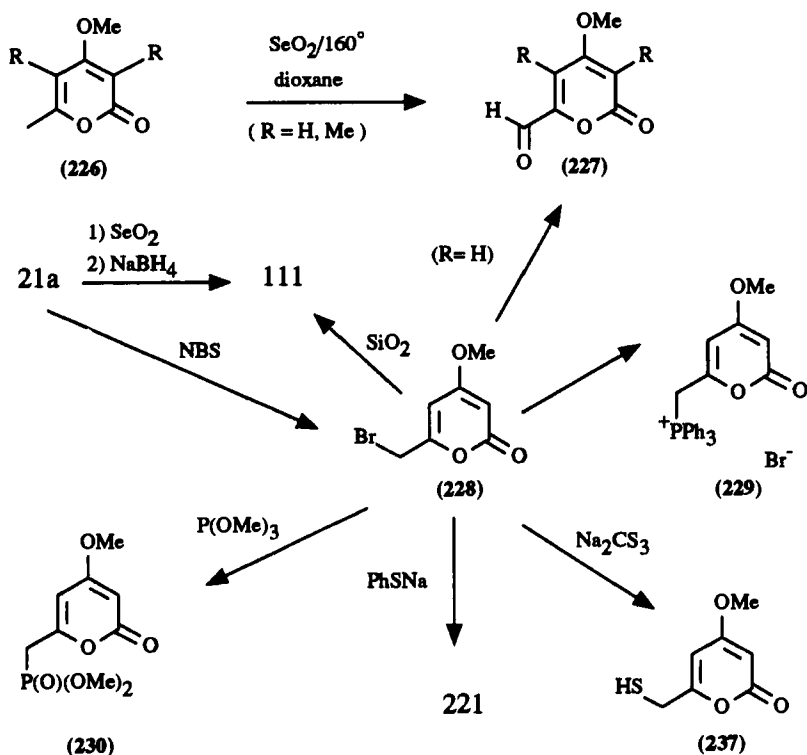
A modification called tandem [2,3] sigmatropic rearrangement of sulfonium ylide—bromine allylic rearrangement has been reported (88JOC5149). Thus, reaction of the C5 brominated 2-pyrone **224** with ethyl diazoacetate under rhodium catalysis results not only in transfer of the ester moiety to C5, as described earlier, but also in the transfer of the bromine atom from C5 to the side chain at C6 in such a way that the functional group remaining at that side chain, as in **225**, can be further elaborated (89JHC1205).

4. *Reactions at the Carbon Atom Linked at C6*

The methyl groups linked at C6 in compounds **2** and **21a** exhibit the normal behavior of allylic positions and can be halogenated under radical conditions and oxidized by appropriate reagents. This is not true for 4-hydroxy compounds with a free C3 position, such as triacetic acid lactone (**1**). In this case, the high activity of C3 dominates the reactivity of **1** and other molecules sharing the same features. However, the methyl group at C6 of **1** can be metallated through the polyanion chemistry developed by Harris to react finally as a strong nucleophile. The methyl ether **21a** and similar compounds offer a rich reactivity, since bromination at the methyl group permits the resulting compounds to react as electrophiles, with the bromide anion acting as a good leaving group. The conversions of the bromides into phosphonium salts and phosphonates open the possibility of the title carbon atom becoming nucleophilic, for instance towards carbonyl compounds. Therefore, this section will treat separately the functionaliza-

tion of the carbon atom near C6, its reactivity as a nucleophile, and its reactivity as an electrophile.

a. *Oxidation, Halogenation, and Formation of other C-X Bonds.* Treatment with selenium dioxide has been the most accepted solution for oxidation. The reaction is regioselective, as shown in the reaction of pyrone **226** (R = Me), possessing three *a priori* reactive methyl groups. The reaction takes place at the methyl group at C6 to afford **227** (R = Me) (75S192). Other similar oxidations have been reported [82JCR(S)224; 85TL4789; 87TL2455]. These reactions are difficult to stop at the alcohol level, but reduction of the aldehyde gives the corresponding alcohol, as in a preparation of the natural product opuntiol (**111**) from **21a** (82JHC157).

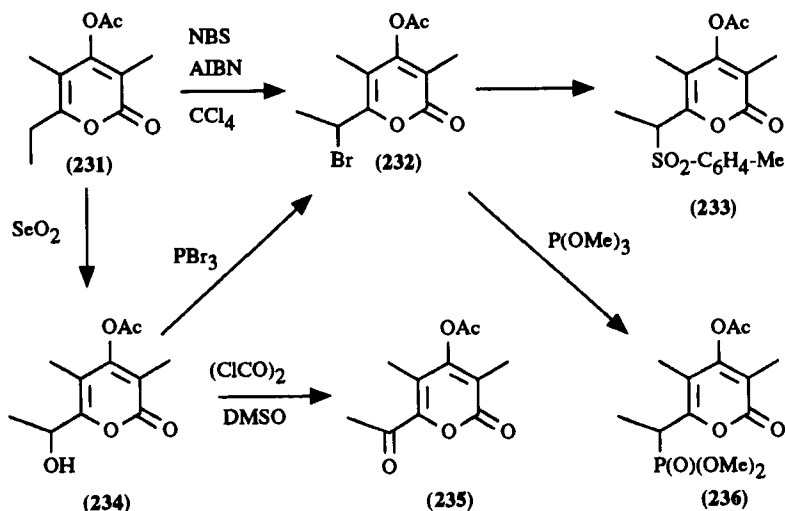


Allylic bromination of **21a** to **228** under radical conditions can be performed, although care must be taken to avoid bromination at C3 [74JOC3615; 82JHC157; 84JCS(P1)1035; 89TL3217]. Conversions of **228** into the phosphonium bromide **229** [74JOC3615; 82JHC157] and the phosphonate **230** [84JCS(P1)1035] are easily performed. Bromination with NBS

and oxidation with selenium dioxide are useful synthetic methods, but they are complemented by the possibility of interconverting both functional groups. Thus, the bromo derivative **228** can be hydrolyzed under very mild conditions into opuntiol (**111**) by stirring with silica gel at room temperature (82JHC157). Several similar allylic brominations and the corresponding hydrolyses have been described (85JHC1537). One case of bromination by quenching a lithio derivative with bromine is exemplified by the transformation of **242** into **243** (89TL3217). Moreover, Kröhnke oxidation of **228** affords **227** ($R = H$). This oxidation has been successfully applied to more complex pyrones (89JHC1205).

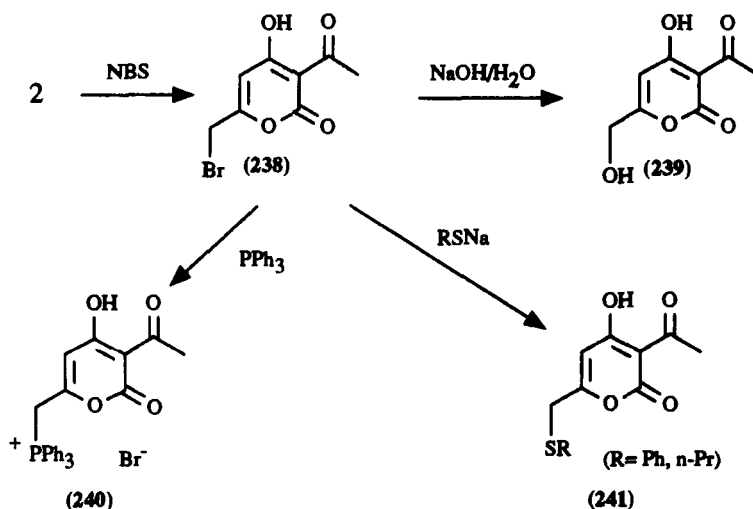
An interesting group of transformations is reported in a single paper (87LA987). Thus, allylic bromination of the 4-acetoxy-2-pyrone **231** affords **232**, which can be converted into **233** and **236** by treatment with sodium 4-toluenesulfinate and with trimethyl phosphite, respectively. Oxidation of **231** with selenium dioxide affords the alcohol **234**, which can be transformed into the bromide **232**. This is an example of the other interchange between the Br and the OH groups; this time the latter is transformed into the former. Further oxidation of **234** affords ketone **235**.

Thiol **237** has been prepared from bromide **228** by treatment with sodium trithiocarbonate (89JHC1205). Sulfides **221** and **224** required for the [2,3]sigmatropic rearrangements in Section V,A,3 are formed by substitution with sodium phenylthiolate from the corresponding bromides such as **228** (84SC521; 89JHC1205).

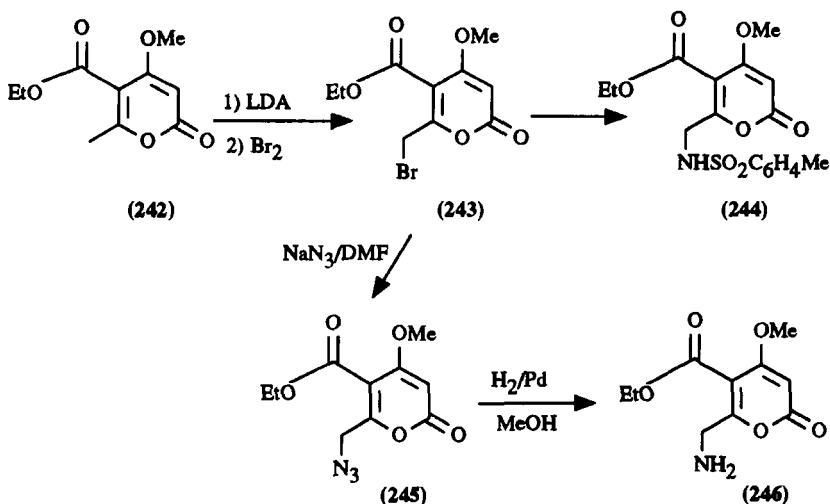


Dehydroacetic acid (**2**) presents a behavior similar to that of ether **21a**, in spite of their structural differences. Thus, allylic bromination leads to

bromide **238** (70JOC1329; 82JHC157), which can be hydrolyzed to alcohol **239** (82JHC157) and transformed into the phosphonium bromide **240** (82JHC157) and into sulfides **241** (89JHC1205).

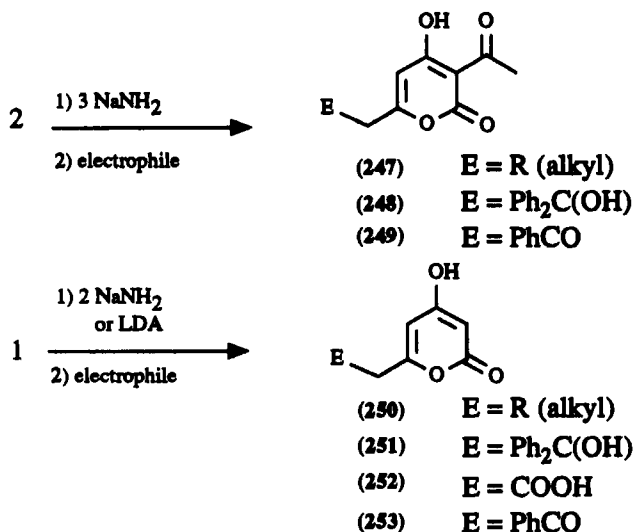


Nitrogen atoms can also be introduced at the side chain at C6. Thus, bromo derivative **243** (from bromination of **242**) was converted into **244** by reaction with the sodium salt of 4-toluenesulfonamide (89TL3217). Also, treatment of **243** with sodium azide leads to the azidopyrone **245**, which, upon hydrogenation, affords the 6-aminomethyl-2-pyrone **246** (89TL3217).



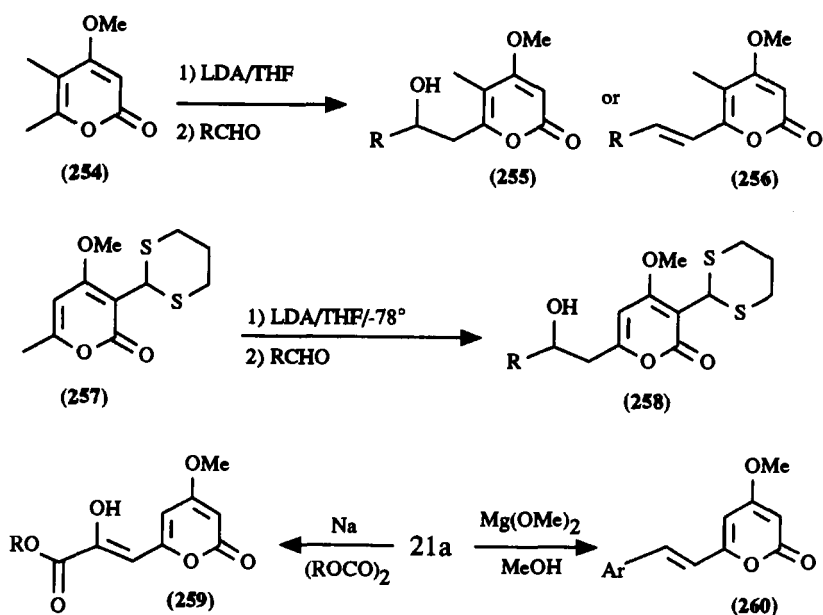
b. *Reactions with Electrophiles.* Treatment of dehydroacetic acid (**2**) with three equivalents of a strong base, such as sodium amide in liquid ammonia, generates the corresponding trianion, which, on quenching with one equivalent of electrophile, affords products **247–249** (68T6897) arising from regioselective reaction at the most nucleophilic carbanionic center: the methyl group at C6. Alkyl halides, benzophenone, and methyl benzoate were reported as electrophiles in the original work by Harris, leading respectively to the indicated final products. This technique has been successfully applied by others, in particular in a synthesis of pheromones (82CL5; 83MI3).

Similarly, treatment of triacetic acid lactone (**1**) with two equivalents of a strong base, such as sodium amide in liquid ammonia or LDA in THF at low temperature, generates the corresponding dianion, which, on quenching with one equivalent of electrophile, affords compounds **250–253** (70T1685); the electrophiles are alkyl halides, benzophenone, carbon dioxide, and methyl benzoate which yield, respectively, the indicated compounds. Other research groups have successfully applied this technique [82CJC2821; 85JHC433, 85JMC1106, 85JMC1828; 86JOC268 (a synthesis of elasinin)]. This is the only reported procedure for reactions of the side chain at C6 in 4-hydroxy-2-pyrones. Under any other experimental conditions, reactions with electrophiles occur at C3 apart from the formation of ethers and esters.



The methyl ether **254** has been reported several times to react with one equivalent of LDA, followed by quenching with aldehydes, to yield

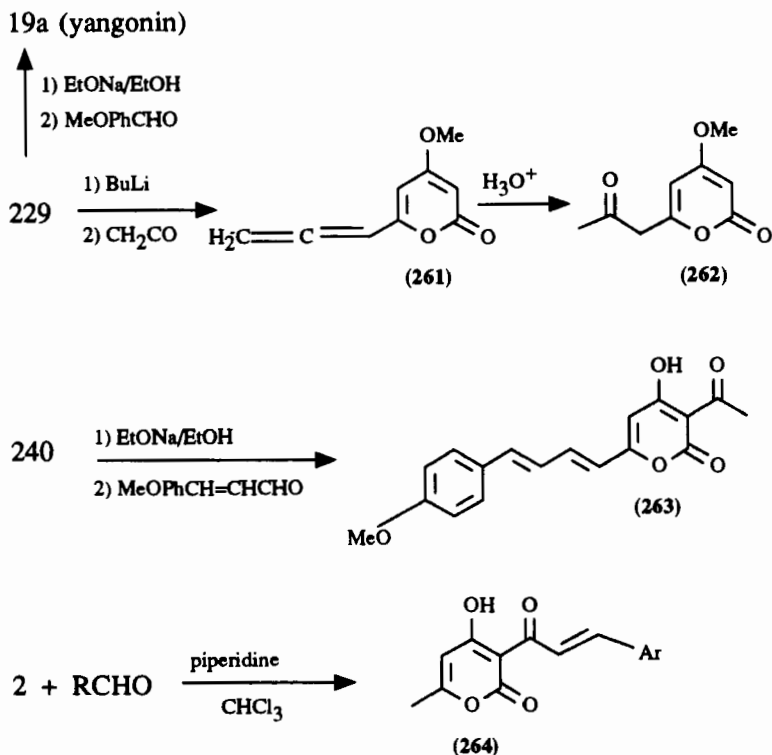
products **255** or **256**. This has been applied to syntheses of citreoviridin (87JOC5067; 88JA470) and asteltxin (84JA4186; 90T2353). Also, the related transformation of **257** into **258** is one step in a synthesis of solanopyrone A (87TL1175). Finally, the reaction of 5-ethoxycarbonyl-4-methoxy-6-methyl-2-pyrone, under similar basic conditions and final reaction with benzyl bromide, also produces benzylation at the methyl group at C6 (89TL3217). Thus, only exceptional reactions occur at C3 under these basic conditions [80CC1227; 91JHC(ip)] (see Section V,A,1,e).



Another reaction that should be included here is the Claisen condensation of **21a** with alkyl oxalates to afford **259** under activation by sodium (68CJC695; 87JMC1017). The reactions of **21a** with aromatic aldehydes in the presence of magnesium methoxide in refluxing methanol constitute a synthetic method widely used to prepare the group of compounds **260** that are either members of the Kawa pyrone family or closely related to them [60JCS502; 67JCS(C)411, 67T3545; 76JOC4070].

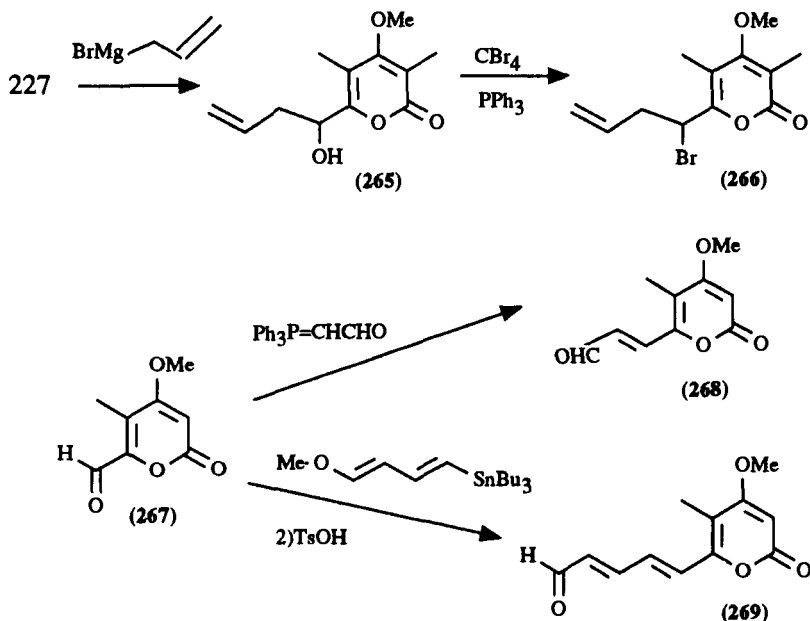
The second obvious way of converting the side chain at C-6 into a nucleophilic center is by means of Wittig chemistry. Thus, the phosphonium bromide **229** has been used to prepare both yangonin (**19a**) (82JHC157) and the methyl ether (**262**) of tetraacetic acid lactone (74JOC3615) by Wittig reactions.

Similarly, Wittig condensation of the ylide derived from the phosphonium salt **240** has been applied to the preparation of **263** and related compounds (82JHC157; 85M15). The Wittig reaction has to be applied in dehydroacetic acid chemistry in order for reactions at the side chain at C6 to take place, because under conventional basic activation, the methyl group at the C3 acetyl group is more active. This is exemplified by the reactions of **2** with aromatic aldehydes, which are a good synthetic method for preparing compounds **264** (55JA5102; 60JCS4395; 73T1083; 80CPB3002, 80CPB3007, 80CPB3013; 89SC3437).



c. *Reactions with Nucleophiles.* Aldehydes generally obtained by selenium dioxide oxidation have been used as electrophilic partners. The reaction of a Grignard reagent with **227** produces **265** in the synthesis of isoareothin (87CL1381). Wittig reagents react with aldehydes at C6. Thus, the transformation of **267** into **268** is a step in the synthesis of citreomontanin (87TL2455). Other reactions with Wittig reagents have

also been reported [75S192; 82JCR(S)224]. Another nucleophilic reagent used for similar purposes is the vinyltin reagent indicated in the conversion of **267** into **269** (85TL4789).



B. REACTIONS THAT MODIFY THE 2-PYRONE SKELETON

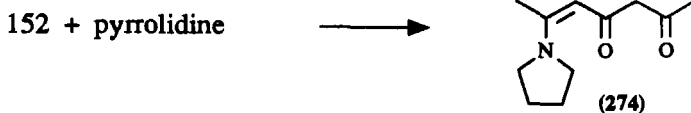
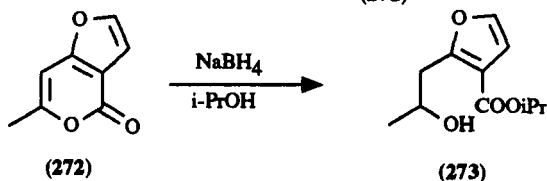
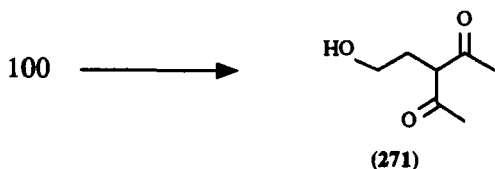
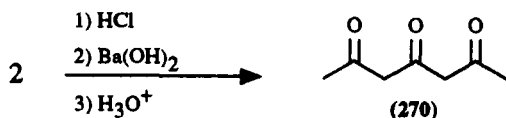
1. Opening of the Ring

Reactions resulting in opening of the pyrone ring without transformation into a different cyclic product are relatively uncommon, although some of them are quite important.

Thus, **1** is opened to ethyl 3,5-dioxohexanoate by the action of ethanol (48JBC485). Dehydroacetic acid can be efficiently converted into methyl 3,5-dioxohexanoate (**32**) by treatment with magnesium methoxide in refluxing methanol (76SC81) in a reaction that occurs with deacetylation. Diketoester **32** is an open polyketide model that can be regioselectively alkylated at C3 and at C5, as indicated in Section III,A. On the other hand, hydrolysis and decarboxylation of **2** affords heptane-2,4,6-trione **270** [62JCS3751; 72JCS(P1)692]. The formation of **271** by alkaline treatment of macommelin-9-ol (**100**) has also been reported (83CPB3781). It is difficult

to ascertain whether these three transformations are initiated by attack at C2 or at C6.

Two reactions with nucleophiles which occur at C6 are the reduction of **272** into **273** (83CB3366) with sodium borohydride and opening of the ring with pyrrolidine in **152**, followed by decarboxylation to afford **274** (70JOC258).

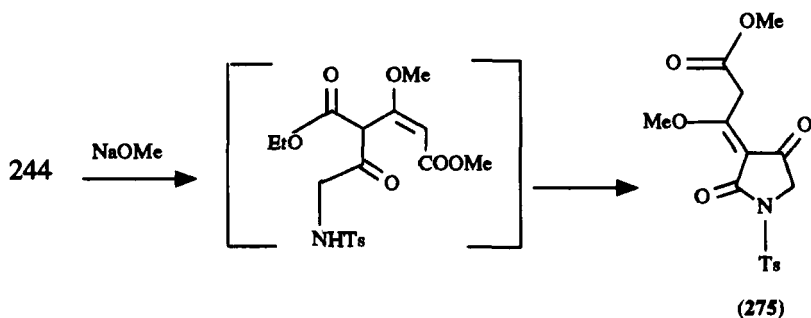


2. Transformations into Other Heterocyclic Systems

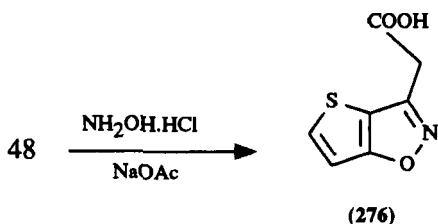
Since open-chain compounds directly arising from opening of 4-hydroxy(or alkoxy)-2-pyrones are highly functionalized, they exhibit a strong tendency to cyclize again, and this can be used to prepare different types of heterocycles. This section is organized according to the type of final heterocyclic ring formed. It is frequently difficult, from the simple examination of chemical structures, to know exactly the bonds broken and formed as well as the external atoms incorporated into the new heterocyclic ring in the transformations dealt with here. To help the reader, we have introduced descriptors in every transformation. Thus, the descriptor C6—C—N/C—C5 for conversion of **224** into **275** means that the nitrogen

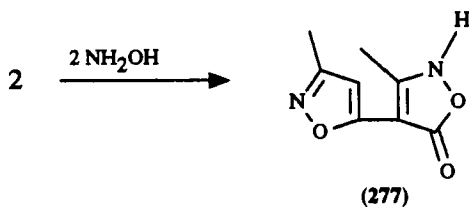
atom (N) linked to the carbon atom (C) linked to C6 of the initial pyrone will be bound, in the final product, to the carbon atom (C) linked at C5 of the initial pyrone. This also indicates that all atoms involved in the transformation were present in the initial product **244**. A different case is illustrated by transformation of **48** into **276**, to which the descriptor C4/N—O/C6 is assigned. This means that an external molecule containing fragment N—O (the reader will guess hydroxylamine or related) has intervened in the reaction. Fragment N—O ends up inserted between carbon atoms C4 and C6 of the initial 2-pyrone ring.

a. *Pyrroles*. Treatment of compound **244** with sodium methoxide forms the acyltetramic acid derivative **275** in a C6—C—N/C—C5 transformation (89TL3217).

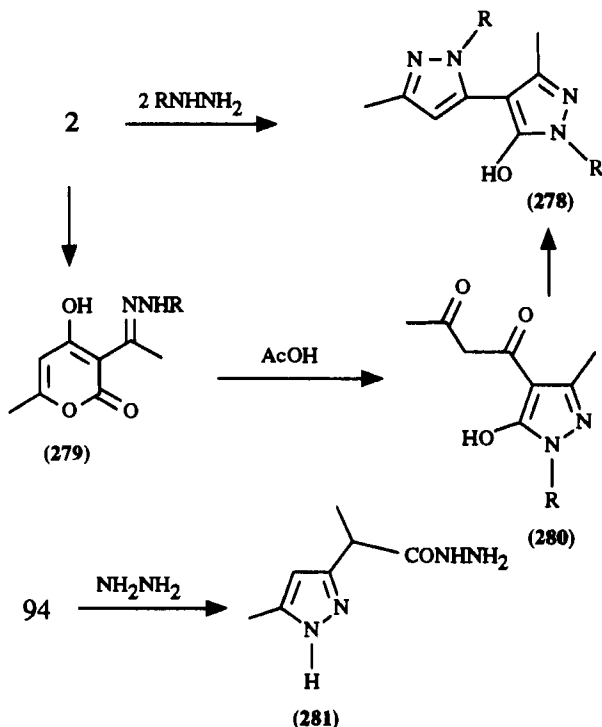


b. *Isoxazoles*. The bicyclic pyrone **48** has been converted into thienoisoxazole **276** by reaction with hydroxylamine in a C4/N—O/C6 process (87AP837). Dehydroacetic acid (**2**) has four electrophilic centers: C2, C4, C6, and the carbonyl group of the acetyl chain. All of them react in the formation of the bis-isoxazole **277** (64CPB381). The overall transformation involves C2/O—N/C—C3 and C4/O—N/C6 steps, where the external N—O fragments are provided by two equivalents of hydroxylamine. This sort of transformation can occur also with hydrazines, as will be shown.



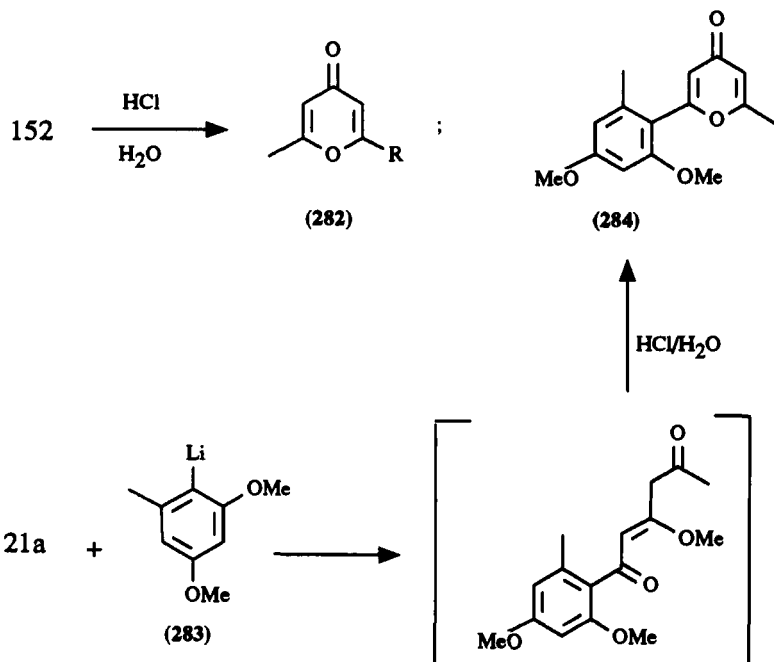


c. *Pyrazoles*. The reactions of **2** with hydrazines have been well studied, and intermediates have been isolated and identified. The final products are bis-pyrazoles **278**, obtained if enough hydrazine is used [77JCS(P1)1428; 87BCJ4425]. The cyclizations involved are of the C2/N—N/C—C3 and C4/N—N/C6 types. The initial step is the formation of the hydrazones **279**, which can be isolated and transformed into acetoacetylpyrazoles **280** (83JOC4078). The tautomeric composition of compounds **280** has been studied (90JHC865). A different transformation (C4/N—N/C6) is the conversion of the natural product **94** into pyrazole **281** (68JA5302).



d. *4-Pyrones*. Hydrolysis of dehydroacetic acid (**2**) and related pyrones of general structure **152** under acidic conditions results in decarboxylation and cyclization to afford 4-pyrones **282** [72JCS(P1)692; 80CPB3002, 80CPB3007]. The process belongs to the C3—C—O/C6 or to the C3—C/O—C6 type, depending on which oxygen atom (lactonic or ketonic) is finally incorporated into the ether bridge of **282**.

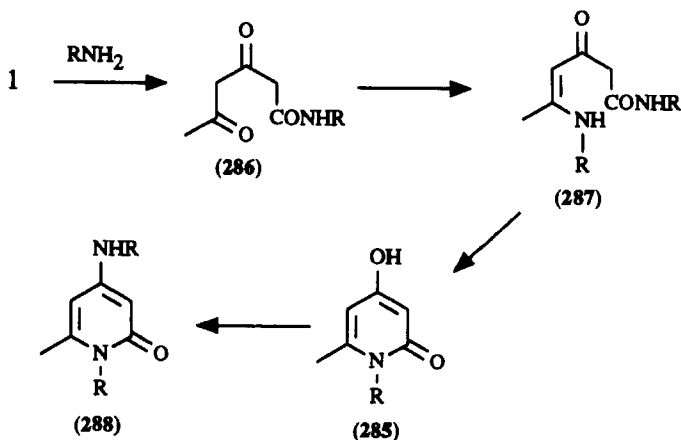
A related transformation is the reaction of carbanion **283** with methyl ether **21a** to afford, after hydrolysis, 4-pyrone **284** [84JCS(P1)1035].



The previously mentioned reaction of **1** with salicylaldehyde to yield pyrones **171** through **173** (86JHC1511; 87T2381) can be included in this section, the overall transformation being of the type C2/O—C—C—C/C3. This sort of process is not uncommon, and similar cases have been described in the patent literature (87EGP252188, 87EGP252604).

e. *Pyridines*. There are many examples of transformations of pyrone **1** into 4-hydroxy-2-pyridones (**285**) by treatment with ammonia and primary amines [63JCS(C)4483; 70JHC389; 75JHC461; 78CR(C)381; 85JMC1106]. The overall process is of the C2/N/C6 type. Investigations on the identification of intermediates have been published. Thus, diketoamide **286**

(R = Ph) [71JCS(C)2721] and **287** (R = Me, Ph, CH₂Ph) [82BSF(2)257] have been isolated. Independent conversion of **285** into **288** has also been reported [82BSF(2)257]. This indicates a ranking of electrophilic reactivity C2 > C6 > C4. However, a different group reported that independent cyclizations of **286** into **285** and into **288** under different experimental conditions occur, but not the transformation of **285** into **288** [71JCS(C)2721].



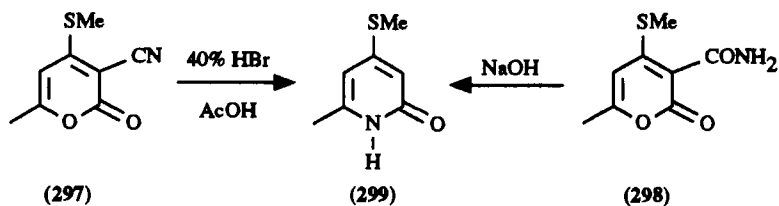
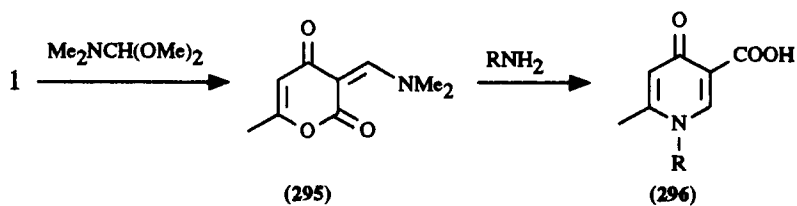
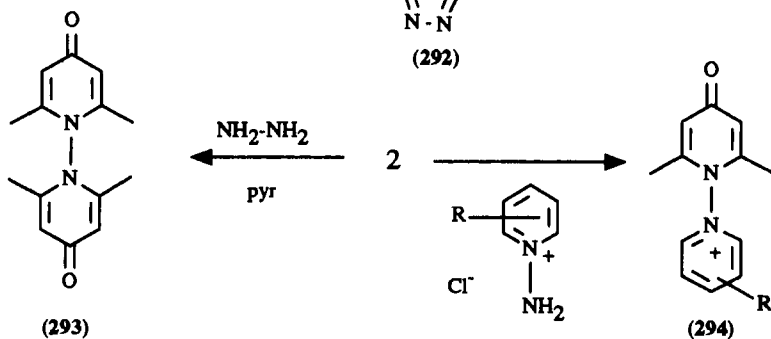
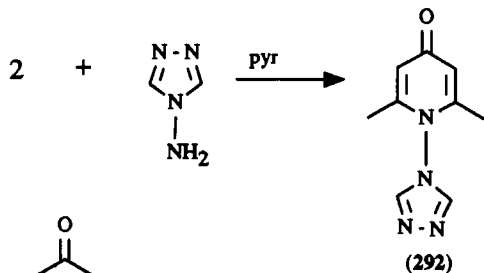
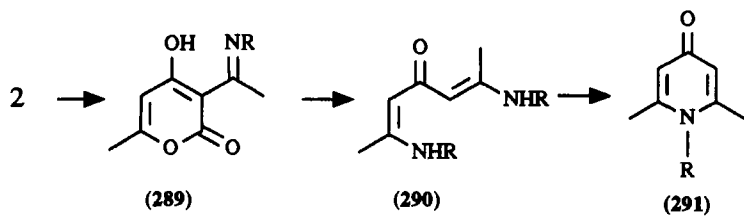
Treatment of dehydroacetic acid (**2**) with ammonia or primary amines affords 2,6-dimethyl-4-pyridones **291** [1885CB452; 71T2581; 78JCS(P1)1373; 88ACS(B)373]. This reaction, of the C3—C/N/C6 type, has been extensively studied, and intermediates **289** and **290** (R = Me) have been isolated and identified (63CJC1435, 63JOC1886).

Interesting versions of this reaction occur with hydrazine and with *N*-amino heterocycles. Thus, reactions of **2** with *N*-amino-1,2,4-triazole, hydrazine, and *N*-aminopyridinium salts produce compounds **292** and **293** [77JCS(P1)1428] and **294** [77JCS(P1)327]. Similar examples have been reported [85JCS(P1)1209].

A different version of the C3—C/N/C6 transformation is exemplified by the conversion of **295** into **296** (72JOC1145; 83MI4; 88MI3), which occurs without decarboxylation.

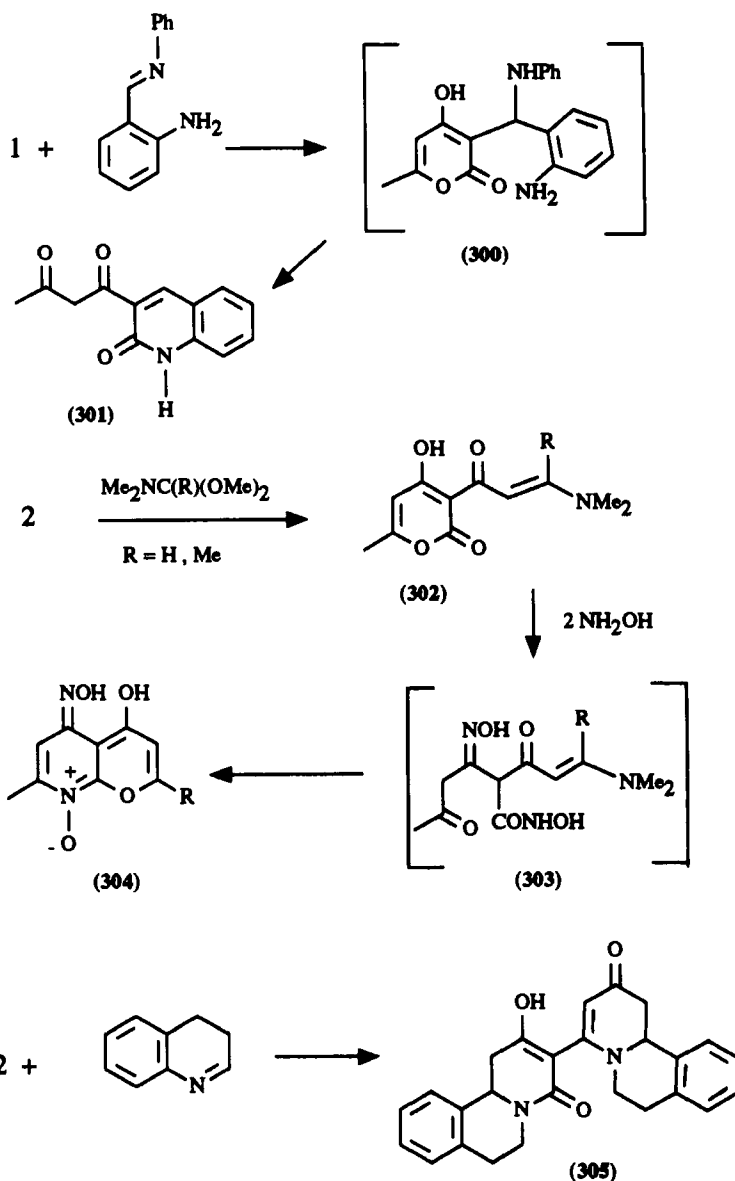
The nitrogen atom of the final pyridone ring can pertain to the initial pyrone as part of the substituent at C3. Thus, a different type of transformation (C3—C—N/C6) has been described, as in the conversions of pyrones **297** and **298** into pyridone **299** (87JHC1325).

The reaction of **1** with the *N*-phenylimine of 2-aminobenzaldehyde affords compound **301**, probably through intermediate **300** (87EGP242805). This reaction, classified as C2/N—C—C—C/C3, underscores once more the



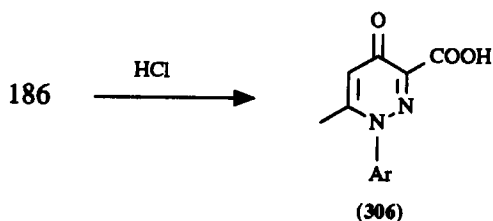
care that should be exercised when assigning structures in the pyrones and pyridones fields.

Formation of products **304** ($R = H, Me$) by reaction of **302** with two equivalents of hydroxylamine (78AP414) and of **305** in the reaction of **2**

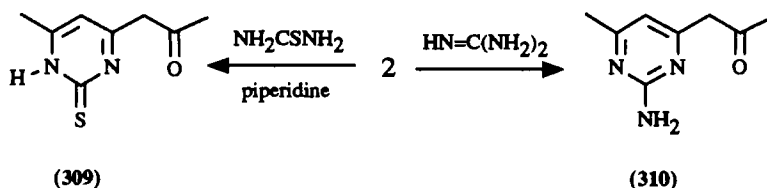
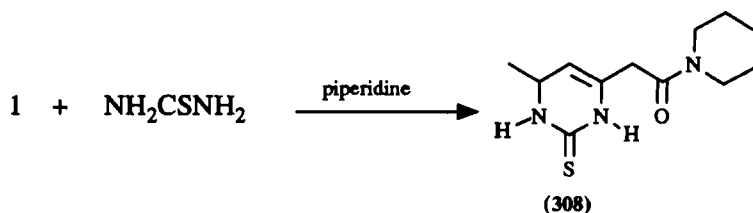
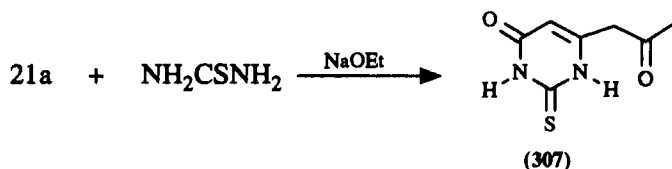


with dihydroquinoline (71IZV1126; 73IZV1302) are good examples of the complexities encountered in opening cyclization sequences.

f. *Pyridazines*. Azo compounds **186** have been transformed into pyridazines **306**. The reaction occurs through a C3—N—N/C6 cyclization and is of possible industrial application (85EUP136974; 88MI3).



g. *Pyrimidines*. Thiourea reacts with both methyl ether **21a** and with **1** to afford compounds **307** (76MI1) and **308** (73MI1), which are formed by C2/N—C—N/C4 and C4/N—C—N/C6 cyclizations. Also, dehydroacetic acid (**2**) has been transformed into **309** and **310** by treatment with thiourea and guanidine (73MI1). Both reactions are of the C3—C/N—C—N/C4 type.



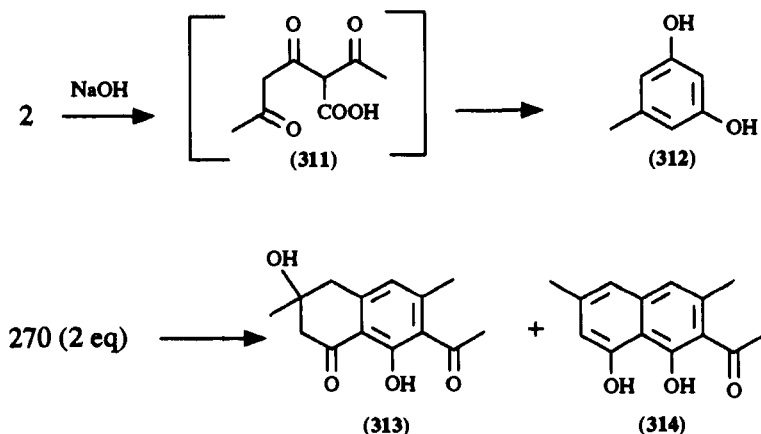
3. Transformations into Carbocyclic Systems

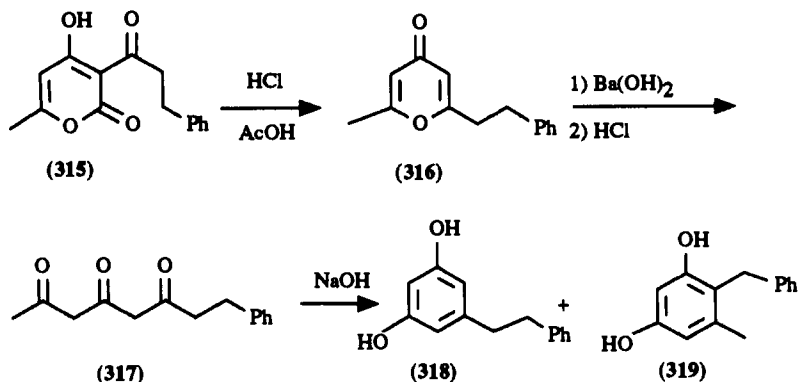
Opening of 4-hydroxy(or alkoxy)-2-pyrones containing no heteroatoms other than oxygen, affords highly functionalized intermediates that, in the absence of reagents bearing heteroatoms, give six-membered carbocyclic rings by means of cyclization processes that sometimes mimic the biogenetic synthesis of phenolic compounds. The reader is referred to a review on the early studies (70CRV553).

The usual reactions involved in carbocyclic cyclization of the aforementioned open-chain intermediates are aldol and Claisen condensations as well as Michael additions. Some examples of the Wadsworth–Emmons reactions have been also published.

Collie reported at the end of the 19th century the conversion of dehydroacetic acid (**2**) into orcinol (**312**) on treatment with sodium hydroxide (1893JCS122). The reaction is a decarboxylative aldol condensation of the C3—C—C/C6 or C3—C/C—C6 type. It is not possible to ascertain at which point decarboxylation occurs. For the sake of simplicity, we have shown the possible intermediate **311** in its acidic form, which is directly related to **2** by simple hydrolytic opening of the ring. However, the decarboxylation product from **311**, namely heptane-2,4,6-trione (**270**), is also a possible intermediate. In independent experiments, triketone **270** was converted into compounds **313** and **314** under nearly neutral conditions by consecutive aldol condensations (1893JCS122; 07JCS1806). Unambiguous assignment of structures **313** and **314** was made much later (60JCS4395; 62JCS3751).

Processes similar to the conversion of **2** into **312** are the low yield preparation of dihydropinosylvin (**318**) and its isomer **319** from pyrone



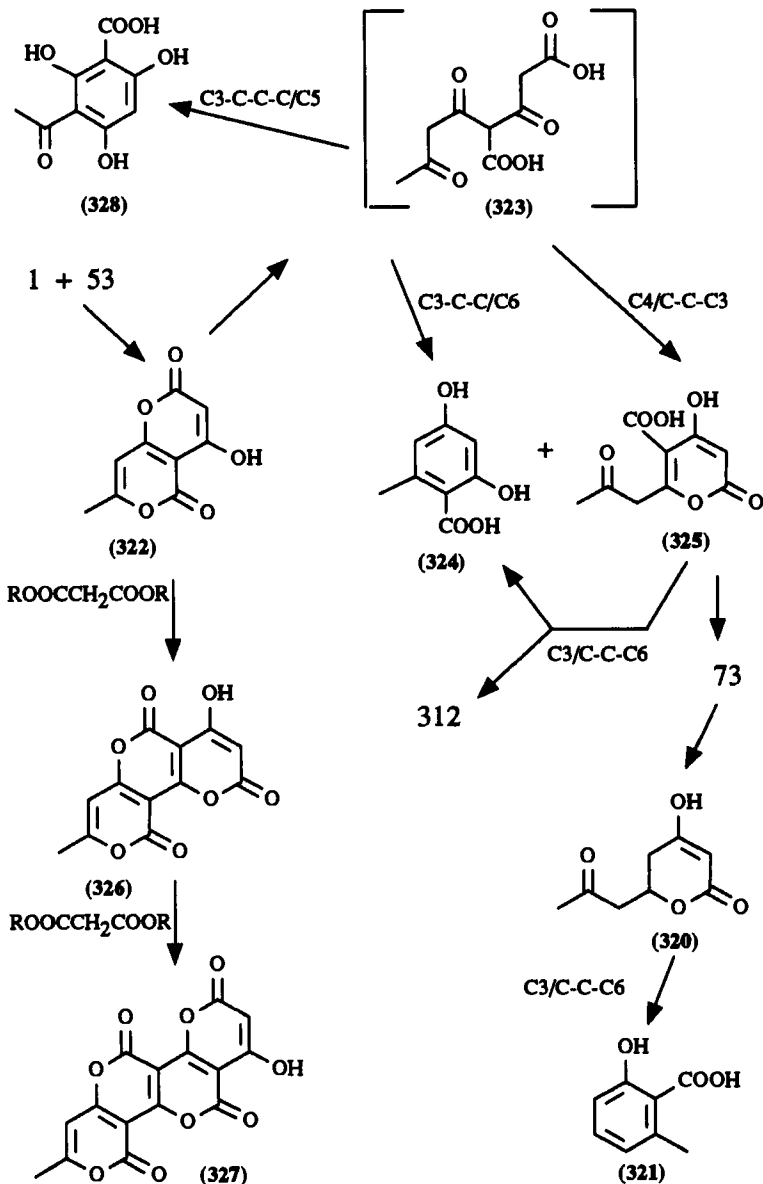


315 (60JCS4395) and of 6-methylsalicylic acid (**321**) from tetraacetic acid lactone (**73**) (68CC1127). The natural pyrone **73** can be prepared by a sequence initiated by the reaction of **1** with malonyl dichloride (**53**), which gives dipyrone **322**. Treatment of **322** with potassium hydroxide produces orsellinic acid (**324**) and mainly the carboxypyrone **325**, which is decarboxylated to **73** (71T3025, 71T3039). Pyrone **325** affords phenols **312** and **324** by base-promoted decarboxylative aldol condensations of type C3/C—C—C6 (71T3025). Similar aldol reactions working with the methyl ether (**262**) of **73** have been reported (71T3039). Preparation of pyrones **326** and **327** by sequential reactions of **322** with malonic acid derivatives has been reported (71T3025).

From the previous discussion, it is evident that intramolecular aldol condensations are commonplace in this field. However, intramolecular Claisen-type condensations can be accomplished by the use of magnesium methoxide, as in the formation of phoroglucinol derivative **328** (70CRV553). The common intermediate **323** (undetermined ionization state) accounts for both formation of **324** through an aldol condensation (C3—C—C/C6) and formation of **328** by Claisen condensation (C3—C—C—C/C5). Further examples of directed cyclizations, depending on the base used, are gathered in the review by Money (70CRV553).

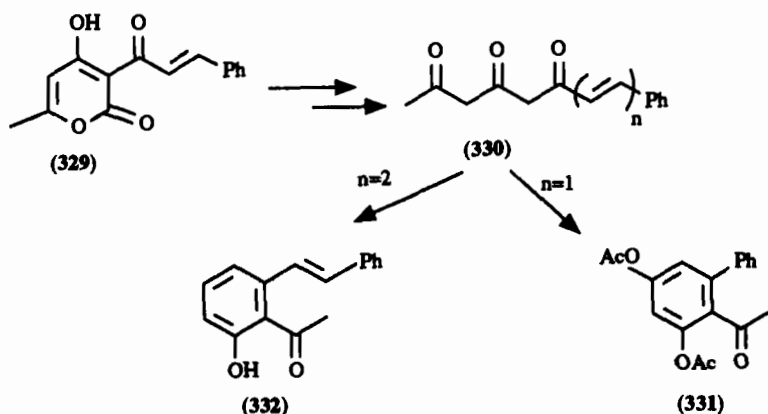
More recent examples of opening of pyrone rings followed by intramolecular aldol (70T5255; 73IZV1122, 73T1083; 76LA1617; 80CPB2460; 81JOC2566; 85MI5) and Claisen (70T5255; 71T3051; 84CB3270) cyclizations have been reported. A special case is an opening-aldol cyclization, which occurred in an acid medium (68T6897).

The presence of adequately placed double bonds allows intramolecular Michael additions to play an important role in carbocyclic ring formations,

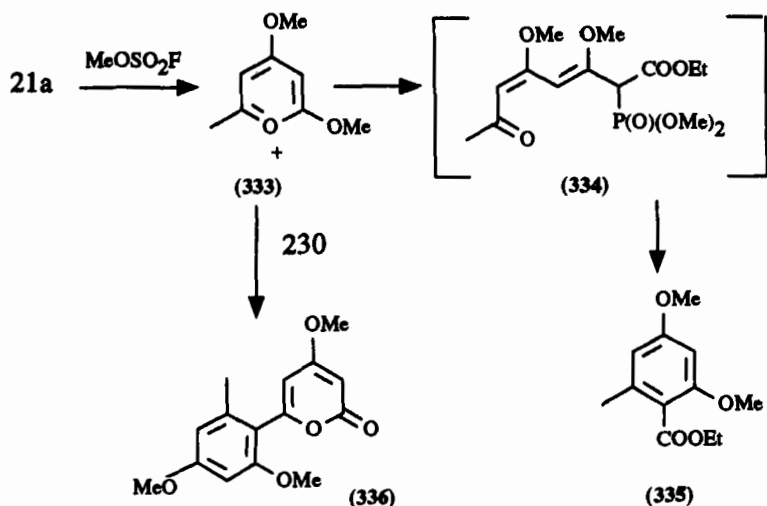


as in the preparation of biphenyl **331** and stilbene **332** (80CPB3002, 80CPB3007, 80CPB3013). The starting pyrones **329** ($n = 1,2$) are converted into **330** by a sequence analogous to that in the transformation of **315** to **317**. Further elaboration includes Michael additions of the

C3—C—C—C/C5 type and complementary steps. Further examples of intramolecular Michael additions have been described (77AP931; 85MI5).

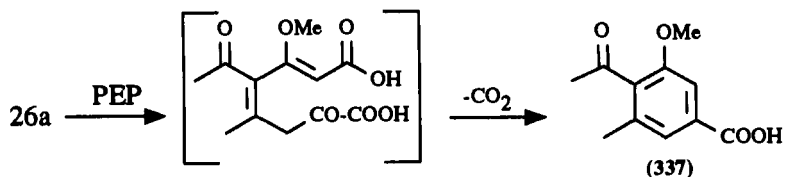


A different strategy has been adopted for the transformation of **21a** into **335** and **336**. In these cases, one carbon atom of the final benzene ring comes from an external phosphonate reagent by means of intramolecular Wadsworth–Emmons reactions. The overall transformations can be classified as C2/C/C6 [84JCS(P1)1035].



An interesting example of biological insertion of carbon atoms C2 and C3 of pyruvic acid between C3 and C6 of pyrone rings (C3/C—C/C6) is performed by *Macrophoma commelinae* on methyl ether **26a** and related

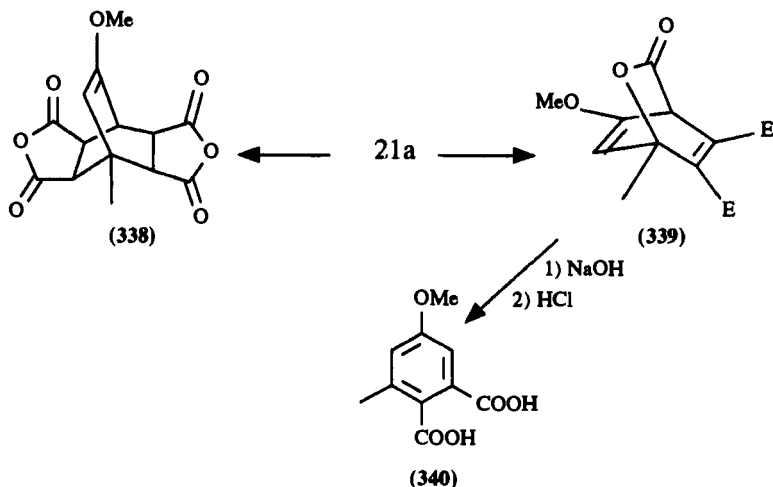
pyrones possessing an electron-attracting group at C5 (88CPB2003). Thus, compound **337** is assumed to be formed by sequential attack at C6 of pyrone **26a**, opening, decarboxylation, and then aldol cyclization (or aldol cyclization and decarboxylation).



C. OTHER REACTIONS

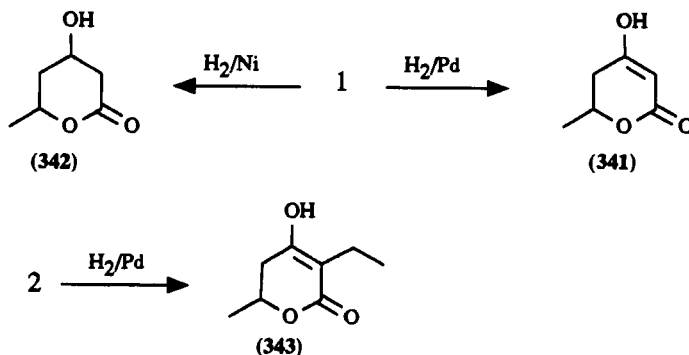
1. Diels–Alder Reactions

Diels–Alder reactions were instrumental in assigning correct structures to both methyl ethers of **1**, formed by treatment with diazomethane. The ether at C4 (**21a**) reacted with both maleic anhydride and with diethyl acetylenedicarboxylate to afford compounds **338** and **339** (60JCS502). Compound **338** arises from a second Diels–Alder reaction of the diene resulting from decarboxylation of the initially formed adduct. Compound **339** was hydrolyzed and decarboxylated to **340**. This synthesis of aromatic compounds has been extensively studied [87CB1339, 87CB1347; 88S383; 90JCS(P1)673, 90JCS(P1)681] as well as used to synthesize the natural pyrenochaetic acid A (87T5245).



2. Hydrogenation of the Ring

Controlled hydrogenation of triacetic acid lactone (**1**) and related pyrones under palladium catalysis leads to selective introduction of hydrogen at the double bond C5=C6, as in the preparation of **341** and related dihydropyrones (57LA58; 60JCS3413; 71T3039; 72IZV917; 78JHC1153; 80TL551; 82CL5; 85CJC1161). Forcing conditions, such as higher pressure under palladium catalysis or nickel catalysis, produce saturation of the ring to afford **342** and related tetrahydropyrones (80TL551; 82CL5). Hydrogenation of the double bond C5=C6 of dehydroacetic acid (**2**) has been described (81JHC543). However, other authors have reported that the partial hydrogenation of the ring is accompanied by reduction of the ketone carbonyl group at C3 to afford compound **343** (56JA3201; 85CJC1161).

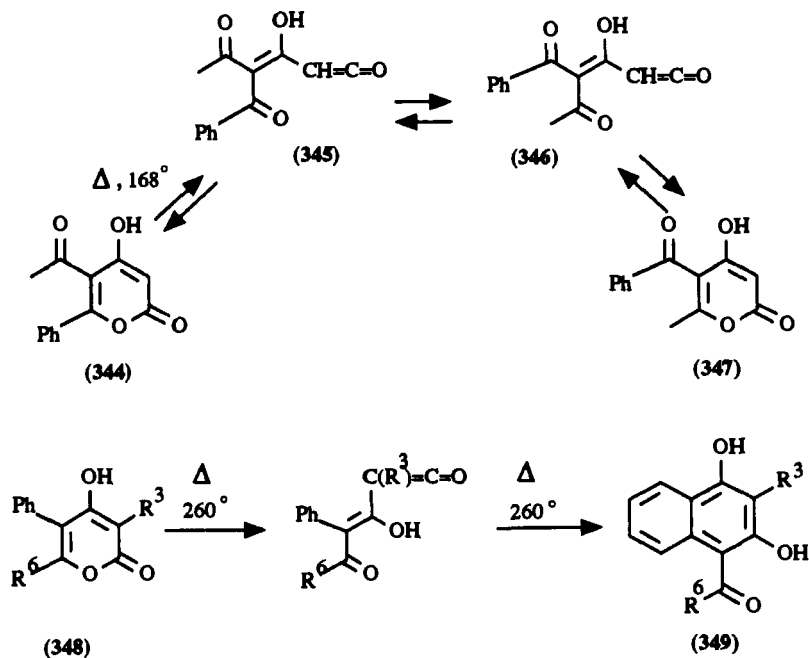


3. Thermal Opening

Pyrones in this review are thermally quite stable. However, forcing conditions can open the pyrone ring. Thus, the curious isomerization of compounds **344** and **347** has been reported to occur through ketenes **345** and **346** (66M1046). Also, compounds **348** ($\text{R}^6 = \text{COOEt}$ and benzyl) rearrange to naphthalenes **349** (79CB2756).

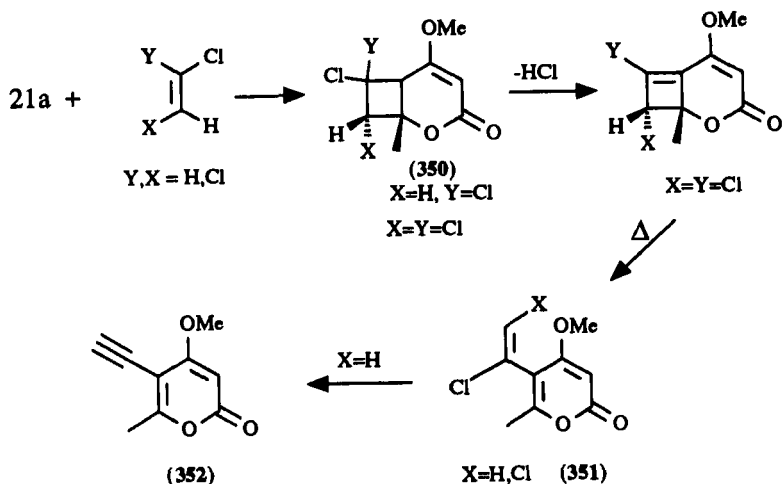
4. Photochemistry

The double bond C5=C6 of the pyrones studied here reacts photochemically with alkenes to afford cyclobutanes. Thus, the reactions of **21a** with olefins afford cyclobutanes **350** ($\text{X} = \text{H}$, $\text{Y} = \text{Cl}$ and $\text{X} = \text{Y} = \text{Cl}$). Further elimination of HCl and rearrangement leads to **351** which finally, if $\text{X} = \text{H}$, results in the acetylenic pyrone **352** (87BCJ621). Dehydroacetic



acid reacts with cyclohexene and vinyl acetate, also forming cyclobutane adducts (73BCJ690).

Some pyrones of the general Kawa structure dimerize on irradiation, even under day light. Although the double bond in the side chain at C6 is,

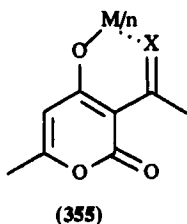
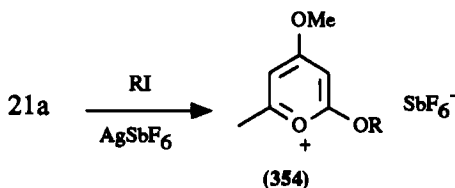
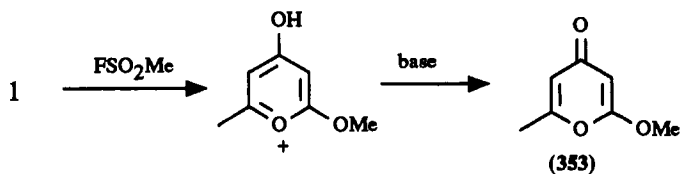


in general, responsible of this behavior, sometimes the double bond at C5=C6 also participates [67JCS(C)413; 72AG(E)479; 82CL741; 83ZN(B)658].

If no olefins are present, triacetic acid lactone **1** and its methyl ether **21a** react photochemically to afford a mixture of compounds without pyrone structure (70CJC237, 70CJC2645).

5. Formation of Ethers at C2

Conventional alkylation conditions on **1** and related pyrones produce ethers at C4. However, their reactions with diazomethane afford ethers at both C2 and C4. The methyl ether at C2 (**353**) can be regioselectively formed and isolated by reaction of **1** with methyl fluorosulfonate followed by neutralization (78JOC1367). Similar reactions on methyl ether **21a** give salts with general structure **354** (64T831; 75T2229).



6. Formation of Metal Complexes

Dehydroacetic acid (**2**) and its Schiff bases are good chelating agents, and many complexes of the general structure **355** ($X = O, NR$) have been synthesized [75MI1; 79BCJ625; 82IJC(A)839; 84MI2; 85MI6; 86MI2; 87IJC(A)887, 87MI1; 88IJC(A)52, 88MI5].

ACKNOWLEDGMENTS

Financial support from Ministry of Education and Science of Spain (DGICyT) through grant PB0030-87 is gratefully acknowledged.

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***N*-Aminoazoles**

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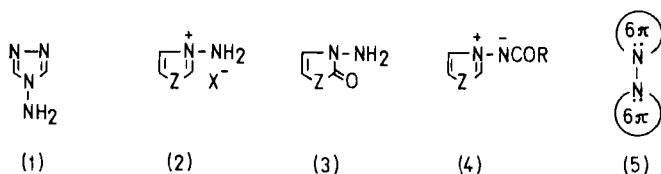
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I. Introduction

The subject of this review is a series of *N*-amino derivatives of pyrazole, imidazole, *v*- and *s*-triazoles, tetrazole, and O- and S-containing azoles. This review also addresses condensed systems, including purines and some peri-condensed azole heterocycles. *N*-Amino derivatives of NH-azoles include both neutral forms (e.g., **1**) and salts (**2**, Z = NR). For



aminooxazoles and *N*-aminothiazoles, the only possible structure is salt (**2**, Z = O, S), although the partially hydrogenated derivatives, for instance **3**, can exist as neutral forms as well. *N*-Aminoazolum salts containing a substituent in the amino group, which increases the NH-acidity (for example, the acyl group), can also give rather stable zwitterions(**4**).

There are two main chronological stages in the development of *N*-aminoazole chemistry (Table I). The first period dates from 1886 to 1915. During that time, the first representatives of the *N*-aminoazole series, mainly triazoles, were synthesized, and the key conversions of this class were investigated. The second period began at the end of the 1950s and receives a large developmental effort at present. This period is marked by the development of the direct methods of N-amination. Due to this, numerous *N*-aminoazoles became available. This period is noted also for the profound study of the chemistry and physical chemistry of *N*-aminoazoles and for the search into a mutual interaction of the azole nucleus and the *N*-amino group. The period from 1915 to 1955 was not marked by intense investigations and great advances and was a dead season in the chemistry of *N*-aminoazoles.

Probably over 50% of all papers on *N*-aminoazoles address the chemistry of *N*-aminotriazoles, especially of 4-amino-*s*-triazole **1**, which is explained by the great availability of these compounds. Many of those papers were published at the beginning of this century, which is why mistakes

TABLE I
CHRONOLOGY OF THE FIRST SYNTHESIS OF SOME N-AMINOAZOLES

Azole	First representative	Parent of the series
Pyrazole	65USP3207763	78TL1291
Indazole-1H	75JCS(P1)31	75JCS(P1)31
Indazole-2H	61JOC3714	72JOC2351
Imidazole	1894CB2203	82S592
Benzimidazole	22JPR102	55JCS2326
<i>v</i> -Triazole-1H	1900CB644 ^a	09CB659 ^b
<i>v</i> -Triazole-2H	67TH1	—
Benzotriazole-1H	1886CB1452 ^a	60MI1
Benzotriazole-2H	65USP3184471	65USP3184471
<i>s</i> -Triazole-1H	63CB2750	80JCR(M)514
<i>s</i> -Triazole-4H	1888JPR531 ^a	1888JPR531 ^a
Tetrazole-1H	14CB1132	60CB850
Tetrazole-2H	69CJC3677	69CJC3677

^a The primary compound was described as a wrong structure.

^b The result was not reinvestigated.

in the determination of structures of the compounds are common. The most common mistake is the description of the compounds not as *N*-aminoazoles, but as the corresponding dihydroazines with the amino nitrogen atom in the ring. Almost all those papers have been reinvestigated, and the mistakes have been corrected. However, there are still some unchecked data, which must be carefully evaluated.

Although the chemistry of *N*-aminoazoles spans a century, it has not yet received an overall treatment; therefore this first review is inevitably rather extensive. However, previous reviews particularly devoted to *N*-aminoazinium salts [81AHC(29)71] and *N*-imines of type **4** [72ZC250; 74AHC(17)213] touched some aspects of the chemistry of *N*-aminoazolum salts. Besides, Beyer summarized his investigation on the chemistry of some *N*-aminoimidazoles (70ZC289), and Molina did the same on syntheses of condensed systems from 4-amino-*s*-triazoline-3-thione (86BSB973).

This review contains a complete set of data on the syntheses, reactions, physical properties, and applications of *N*-aminoazoles of types **1–4**. Within this rigorous scope, *N,N'*-bihetaryls (**5**) and the other compounds with the tertiary *N*-amino group must also be included with *N*-aminoazoles. Therefore, such compounds are also taken into consideration in this review. The chapter covers references published up to December, 1989. The names and structural formulas of tautomeric compounds are given, as a rule, according to their predominant structures (76M12), which may be not in agreement with the data given in the primary references.

II. Synthesis

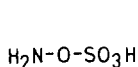
A. GENERAL CONSIDERATIONS

There are five general methods for obtaining *N*-aminoazoles:

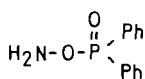
- (1) Cyclization of suitable acyclic compounds (usually hydrazine derivatives)
- (2) Transformation of hetero-rings (recyclization)
- (3) Electrophilic amination of azoles
- (4) Functionalization of the *N*-aminoazoles
- (5) *N*-Amination of the azole nucleus via a nitrene.

The last method is very specific, and as will be seen, it is essentially useful only for its intramolecular version. The other methods are almost

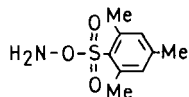
universal, and each has its own field of application and importance. The most attractive route appears to be the direct electrophilic N-amination. For this purpose, the following aminating agents are used: Chloroamine, hydroxylamine-*O*-sulfonic acid (HOSA) **6**, diphenylphosphinylhydroxylamine (DPPH) **7**, *O*-mesitylsulfonylhydroxylamine (MSH) **8**, *O*-dinitrophenylhydroxylamine (DNPH) **9**, and *O*-*p*-tolylsulfonylhydroxylamine (TSH) **10**.



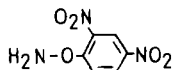
(6)



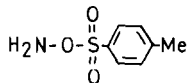
(7)



(8)



(9)



(10)

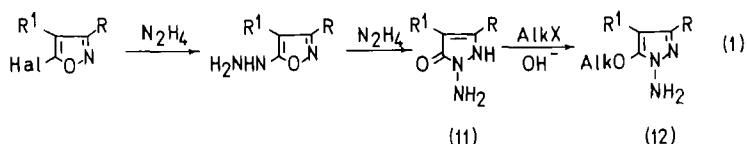
The most available and therefore the most widely used aminating agent is HOSA, obtained from hydroxylamine and oleum (82OPP265). However, it has some drawbacks. First, it can be used in aqueous media, but only occasionally in aqueous alcohol or in dimethylformamide (DMF), and in the latter cases, yields of *N*-aminoazoles are lower. Second, HOSA is readily decomposed by water and especially by alkali, and its anion, which takes part in the reaction, is not very electrophilic. For these reasons, HOSA does not give satisfactory results on amination of sterically hindered and slightly nucleophilic N-anions.

Syntheses of **7–10** were described in references [82S592; 77S1; 73JOC1239; 76JCS(P1)367], respectively. These methods are not particularly easy, and occasionally the danger of explosion exists. However, these drawbacks are offset by the possibility of using these aminating agents in nonaqueous media, where it is possible to use bases stronger than NaOH, for instance sodium hydride. This is important for the amination of the azoles of low NH-acidity. Besides, compounds **7–10** possess a higher electrophilicity than HOSA. This is especially true for MSH, which is widely used for amination of neutral azoles affording *N*-aminoazolum salts (77S1).

B. *N*-AMINOPYRAZOLES1. *Noncondensed Pyrazoles*

Almost all *N*-aminopyrazoles were obtained by the amination of pyrazole or its derivatives with HOSA or MSH (Table II). Only on formation of 1-amino-3,5-dimethylpyrazole having the ^{15}N label was labeled chloroamine used. As a rule, yields of *N*-aminopyrazoles are rather high, but with an increase in the number and size of substituents on the ring, yields decrease. 3(5)-methyl- and 3(5)-aminopyrazoles are aminated with the formation of a nearly inseparable mixture of 1-NH₂-3-R- and 1-NH₂-5-R-pyrazoles in a $\sim 1:1$ ratio. However, if the substituent at position 3 is more bulky, the main or even the dominant component in the mixture is 1-NH₂-3-R-pyrazole (compare for, instance, data for 3-ethyl- and 3-phenylpyrazoles in Table II). No doubt, this is the result of steric interference by the substituent.

On amination of 1,3,5-trimethyl- and 1,3,4,5-tetramethylpyrazoles with MSH, the corresponding *N*-aminopyrazolium salts were obtained (76CPB2267). The formation of *N*-aminopyrazoles by a recyclization reaction was described. Thus, on heating 5-halogeno- or 5-hydrazinoisooxazoles in anhydrous hydrazine, 1-aminopyrazol-5-ones (**11**) are formed; those can be converted further by various alkylating agents into 1-amino-5-alkoxypyrazoles (**12**) [Eq. (1)] [72JHC1219; 76USP3944563; 77JCS(P1)971; 81FRP2479219; 84JHC627].



Gilchrist *et al.* used the reaction of inverse azadiene synthesis to obtain 1-phthaloylaminopyrazoles (**14**) from tetrazole (**13**) and activated acetylene compounds [73CC819; 75JCS(P1)1747]. Heating 1-*o*-nitrophenylpyrazoles with triethylphosphite leads to pyrazolo[1,2-*a*]benzotriazoles [Eq. (2)]

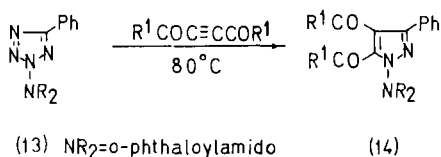


TABLE II
N-AMINOPYRAZOLES OBTAINED BY DIRECT AMINATION OF PYRAZOLES

$ \begin{array}{c} \text{R}^1 \quad \text{R} \\ \diagdown \quad \diagup \\ \text{C} = \text{N} - \text{N} \\ \diagup \quad \diagdown \\ \text{R}^2 \quad \text{NH}_2 \end{array} $					
R	R ¹	R ²	Aminating agent	Yield %	Footnotes
H	H	H	HOSA	52, 99, 40	<i>a, b, c, d</i>
H	H	H	MSH	90	<i>e</i>
Me	H	H	HOSA	93 ^{<i>j</i>}	<i>b</i>
H	H	Me	HOSA	93 ^{<i>j</i>}	<i>b</i>
Me	H	H	MSH	85 ^{<i>j</i>}	<i>e</i>
H	H	Me	MSH	85 ^{<i>j</i>}	<i>e</i>
H	Me	H	HOSA	79	<i>b</i>
H	Me	H	MSH	77	<i>e</i>
Me	H	Me	HOSA	24	<i>b</i>
Me	H	Me	MSH	91	<i>e</i>
Me	H	Me	¹⁵ NH ₂ Cl	—	<i>f</i>
Me	Me	H	HOSA	16	<i>b</i>
Me	Me	Me	HOSA	18	<i>b</i>
Me	Me	Me	MSH	67	<i>e</i>
—(CH ₂) ₄ — —(CH ₂) ₅ —	Me	H	HOSA	69	<i>g</i>
		H	HOSA	66	<i>g</i>
		H	HOSA	30	<i>b</i>
Ph	H	H	MSH	45	<i>e</i>
H	H	Ph	MSH	6	<i>e</i>
H	Ph	H	HOSA	31	<i>b</i>
Ph	H	Ph	HOSA	34	<i>b</i>
Ph	H	Ph	MSH	56	<i>e</i>
Ph	Ph	H	HOSA	31	<i>b</i>
Ph	H	Me	MSH	52	<i>e</i>
Me	H	Ph	MSH	13	<i>e</i>
Ph	Ph	Ph	HOSA	41, 76	<i>b, f</i>
Et	H	H	HOSA	91	<i>b</i>
CH ₂ OH	H	H	HOSA	74	<i>b</i>
CO ₂ H	H	H	HOSA	51	<i>b</i>
Ph	CO ₂ H	H	HOSA	76	<i>b</i>
H	H	NH ₂	HOSA	13	<i>h</i>
NH ₂	H	H	HOSA	10	<i>h</i>
Ph	H	NH ₂	HOSA	30 ^{<i>j</i>}	<i>h</i>
NH ₂	H	Ph	HOSA	30 ^{<i>j</i>}	<i>h</i>
H	Cl	H	HOSA	—	<i>i</i>
H	NO ₂	H	HOSA	—	<i>i</i>
Br	Br	Br	HOSA	—	<i>i</i>
CN	CN	NH ₂	HOSA	—	<i>i</i>

^a (78TL1291)

^b (85LA1732)

^c (87AP115)

^d (83H1271)

^e (85JOC5520)

^f [86JCS(P1)1249]

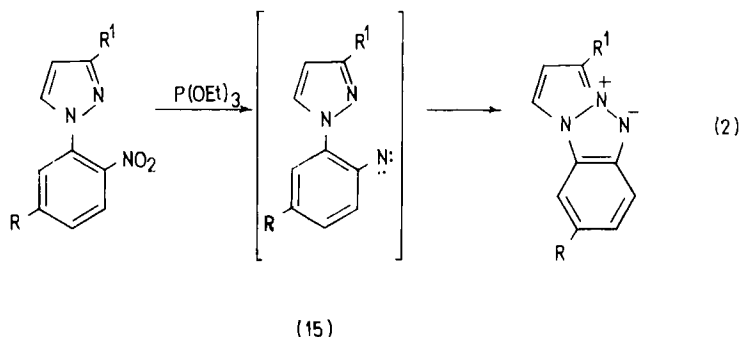
^g (86H907)

^h (86S71)

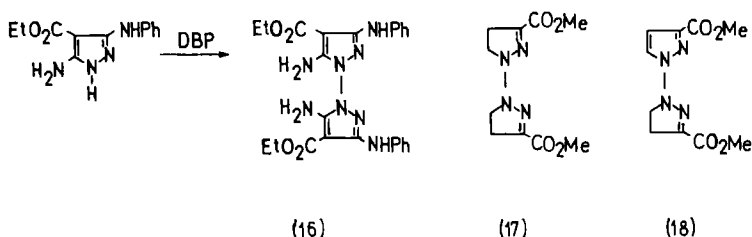
ⁱ (65USP320763)

^j The mixture of two isomers was not separated.

[65JHC218; 80JCS(P1)982]. Judging by the influence of substituents on the ease of this intramolecular amination, the process occurs via nitrene **15**. The yield of the final product is higher when the electron-withdrawing effect of R and the electron-donor effect of R' are greater.



There is little data on *N,N'*-dipyrazoles. The information of Auwers *et al.* (25LA54) about the interaction of bromine with the silver salt of 7-methyltetrahydroindazole and the formation of the corresponding 2,2'-dimer was not supported (85H2629). However, Schulz and co-workers obtained *N,N'*-dipyrazolyl **16** through oxidation of 5(3)-amino-3(5)phenylamino-4-ethoxycarbonylpyrazole by benzoyl peroxide or by di-*tert*-butyl peroxide (82JPR309, 82ZC56). De Mendoza *et al.* investigated oxidation of 3-methoxycarbonyl- Δ^2 -pyrazoline with the hope of obtaining more simple *N,N'*-dipyrazoles (85H2619). Dimers **17** and **18** having a pyrazoline structure were isolated in low yield.



2. Indazoles

Indazoles are aminated by HOSA in alkaline media, affording an easily separated mixture of 1- and 2-aminoindazoles [Eq. (3)]; the 1-amino derivative (Table III) usually predominates. By the action of MSH on 1-methyl-

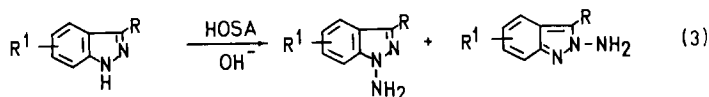
TABLE III
AMINATION OF INDAZOLES BY HOSA^a

Initial indazole	% Yield	
	1-NH ₂	2-NH ₂
Unsubstituted	50	33
3-Methyl-	45	30
3-Phenyl	60	8
3-Methoxy- ^b	88	—
5-Nitro-	57	9
6-Nitro-	30	28

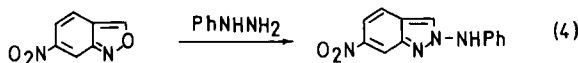
^a [75JCS(P1)31]

^b The aminating agent is chloroamine.

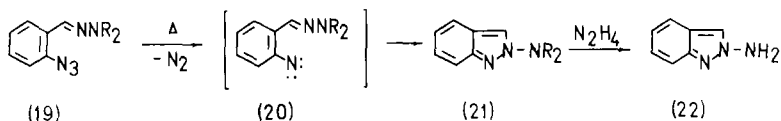
and 1,3-dimethylindazoles, 2-amino-1-methyl- and 2-amino-1,3-dimethyl-indazolium mesityl sulfonates were obtained (76CPB2267).



A series of methods based on cyclization and recyclization reactions was proposed for synthesizing *N*-aminoindazoles. These reactions are mainly concerned with 2-alkylamino- and 2-dialkylaminoindazoles. However, occasionally compounds with 2-unsubstituted amino group can be obtained. The first known example of an *N*-aminoindazole is 2-phenylamino-6-nitroindazole, obtained on heating 6-nitroanthranyl with phenylhydrazine [Eq. (4)] (61JOC3714).

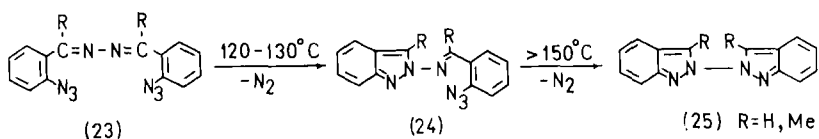


Most other methods are based on *o*-azido or *o*-nitro derivatives of aromatic aldehydes and ketones. Thus, thermolysis of *o*-azidobenzalhydrazone (**19**) protected by the *o*-phthaloyl group leads to 2-phthaloylamindazole (**21**), which, under the action of hydrazine, affords 2-aminoindazole (**22**). Both stages give almost quantitative yields. Supposedly, this reaction takes place via nitrene **20**. In contrast to amine **22**, 2-amino-3-methylindazole can be obtained in a yield of 80% in one step on heating 2-azidoacetophenone hydrazone (72JOC2351).



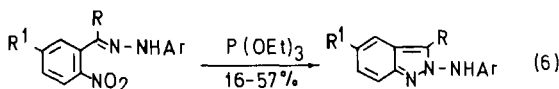
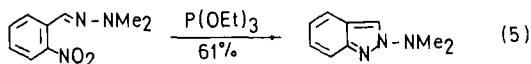
NR₂ = *o*-phthaloylamido

Thermolysis of diazides **23** occurs as a two-step process. Thus, at a temperature of 120–130°C, 2-aminoindazole hydrazone **24** is formed, and this compound can be isolated. At elevated temperatures, the second pyrazole ring is closed and 2,2'-biindazolyis **25** are formed (64JOC1150).

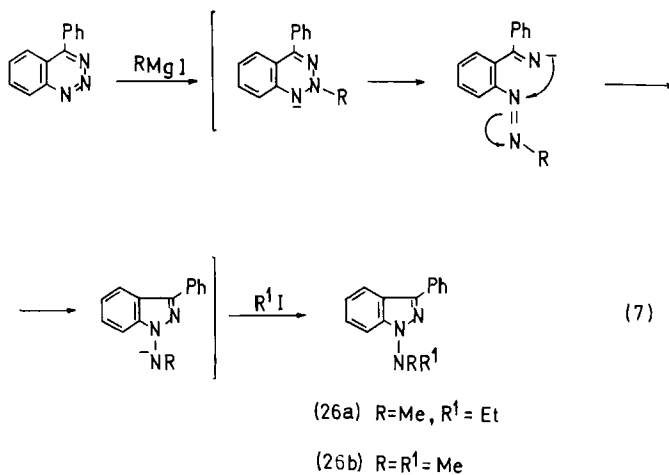


With the help of this method based on mixed bihydrazones, one can synthesize unsymmetrically substituted 2,2'-diindazolyis, for instance, 3,7'-dimethyl-2,2'-diindazolyl (88JOC2055).

Equations (5) and (6) demonstrate another kind of nitrene synthesis of 2-aminoindazoles, where the initial compounds are *o*-nitroarylhydrazones (73S363). This method was also used to synthesize 2,2'-diindazolyl (65JCS4831).

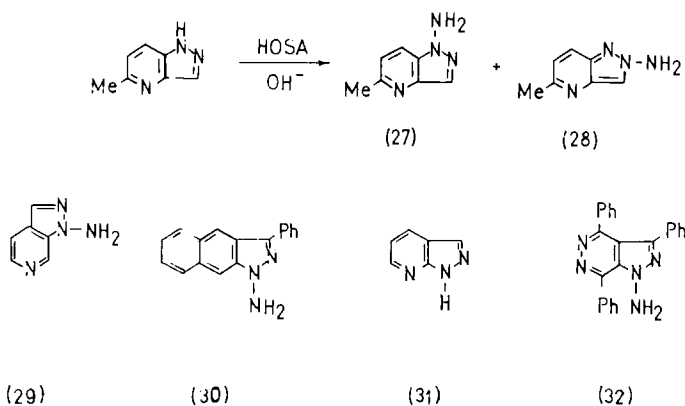


The only synthesis of 1-dialkylaminoindazoles is based on a recyclization reaction (83CC1344). Under the action of ethylmagnesium iodide on 4-phenylbenzo-1,2,3-triazine followed by treatment with methyl iodide, the formation of 1-aminoindazole **26a** in 44% yield was observed. The same compound (23% yield) with a small amount of amine **26b** is formed when methylmagnesium iodide and ethyl iodide are taken instead of ethylmagnesium iodide and methyl iodide. Supposedly, the reaction occurs as shown in Eq. (7).

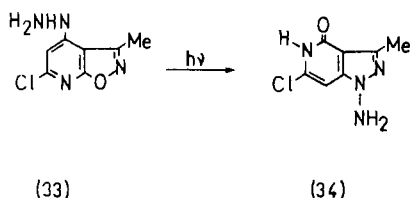
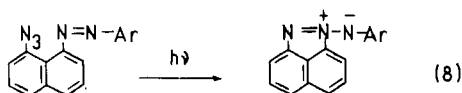


3. Other Pyrazole Systems

Besides *N*-aminoindazoles, there are *N*-amino derivatives of some other condensed pyrazole systems. Most were obtained on electrophilic amination of the corresponding heterocycles by HOSA [75JCS(P1)31]. For instance, on amination of 5-methylpyrazolo[4,3-*b*]pyridine, 1- and 2-amino derivatives **27** and **28** are formed in yields of 42 and 40%, respectively. Similarly, amines **29** and **30** were obtained, whereas amination of pyrazolo[3,4-*b*]pyridine (**31**) failed.



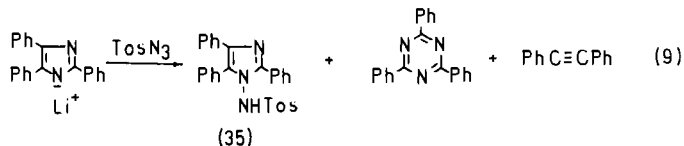
Amine **32** was obtained on interaction of compound **14** ($R' = \text{Ph}$) with hydrazine; closure of the pyrazine ring and withdrawing of the phthaloyl protection are simultaneous processes. Photolysis or thermolysis of 1-aryldiazo-8-azidonaphthalenes gives rise to benzo[*c,d*]indazole *N*-arylimines (78JOC2508 [Eq. (8)]. As a result of a complicated photochemical rearrangement, isoxazolo[5,4-*b*]pyridine derivative (**33**) is converted to *N*-aminopyrazole **34** in 60% yield (88H1899).



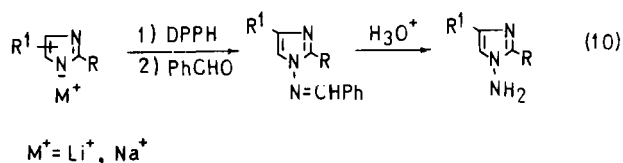
C. *N*-AMINOIMIDAZOLES

1. *Noncondensed Imidazoles*

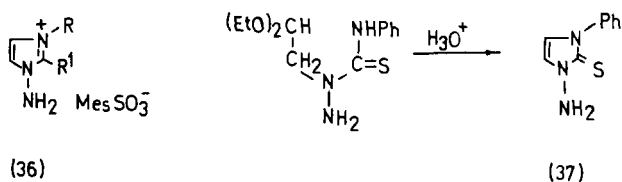
The scope of direct amination reactions is not too great in comparison with all other methods for synthesizing simple *N*-aminoimidazoles. Probably the first specific example of *N*-amination of imidazoles was the synthesis of 1-tosylamino-2,4,5-triphenylimidazole on treatment of the lophine anion with tosylazide [Eq. (9)] (72BCJ306). However, the yield of **35** was small because of the side formation of 2,4,6-triphenyl-1,3,5-triazine and diphenyl acetylene.



Klötzer and co-workers reported in 1982 a successful amination of an imidazole and its 2-nitro and 2-methyl-4(5)-nitro derivatives with the use of *O*-diphenylphosphynyl hydroxylamine [Eq. (10)] (82S592). The reaction was carried out by the action of DPPH on a sodium or lithium salt of the corresponding imidazole in *N*-methylpyrrolidone media. The product was isolated as an *N*-benzylideneamino derivative, then hydrolyzed to the unsubstituted *N*-amine. Since the parent of the series, 1-aminoimidazole, is unstable, this compound was isolated only as its hydrochloride. All attempts made by the authors of this review to synthesize 1-aminoimidazole by amination of imidazole with HOSA in alkaline media led to resinification and regeneration of the initial compound.

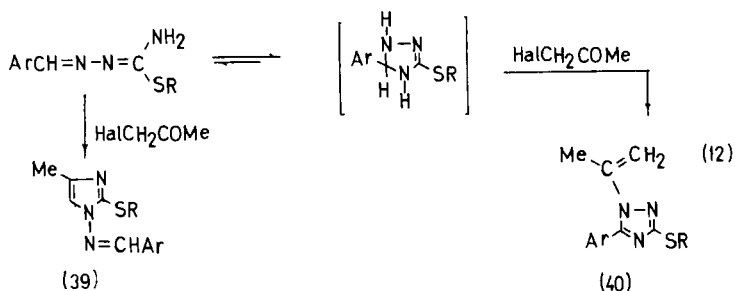
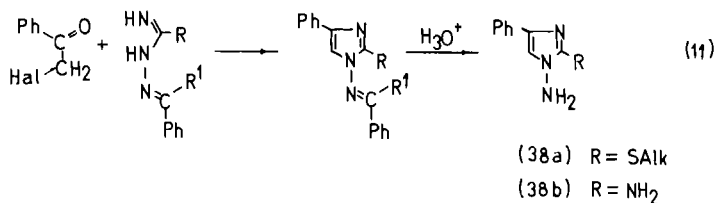


N-Aminoimidazolium salts **36** were obtained in good yield on short-term heating of 1-*R*-imidazoles and MSH in methylene chloride (74CPB482; 74JHC781). All other methods of obtaining of *N*-aminoimidazoles are based on cyclization and recyclization reactions. Thus, at the end of the last century Fischer *et al* synthesized 1-amino-3-phenylimidazoline-2-thione (**37**) in 45% yield by cyclization of 2-(2,2-diethoxyethyl)-4-phenylthiosemicarbazide in acid (1894CB2203).

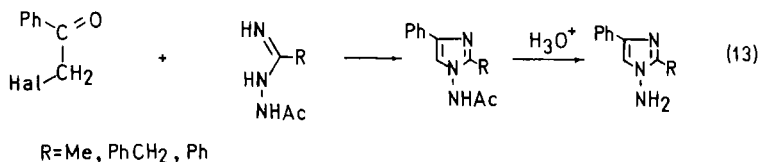


Hydrazones of isothiosemicarbazide (72CL617; 78BCJ1846, 78TL1295) and aminoguanidine (68CB3151; 73KGS1190; 82KGS236) are the initial compounds used to synthesize 1-amino-2-alkylthioimidazoles (**38a**) and 1,2-diaminoimidazoles (**38b**), respectively [Eq. (11)]. Desylchloride, α -halogenalkylarylketones, α -halogenacetones, and α -halogenaldehydes can be used instead of phenacylhalides in these conversions, resulting in 4(5)-alkyl, 4,5-diaryl- and 4(5)-alkyl-5(4)-aryl derivatives of *N*-aminoimidazoles. However, the interaction of α -halogenacetones with isothiosemicar-

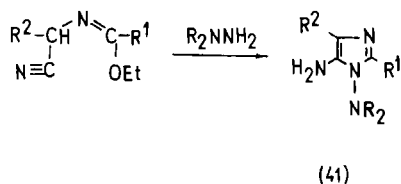
bazide hydrazones leads to a mixture of *N*-aminoimidazole **39** and *N*-isopropenyl-1,2,4-triazoles **40** [Eq. (12)]. In the case of α -bromoacetone, the yield of *N*-aminoimidazole is higher, whereas the use of α -chloroacetone gives rise to triazole **40** as the main product (78TL1295).



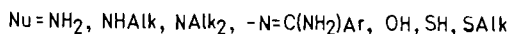
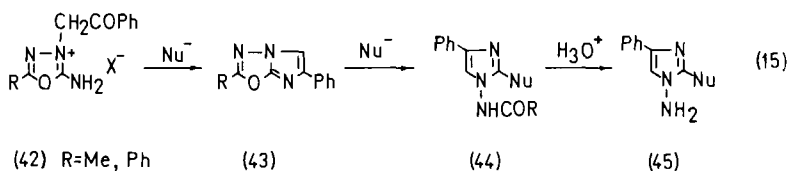
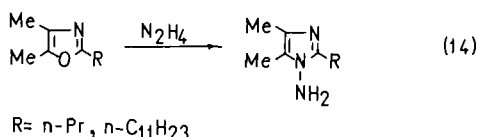
A very convenient method for obtaining 2-alkyl- and 2-aryl-1-aminoimidazoles is the interaction of *N*-acetylamidrazones with phenacylhalides [Eq. (13)] [72JCS(P1)2927].



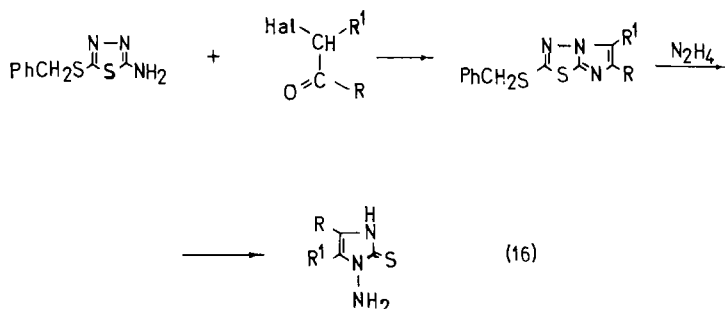
The general method of synthesizing 1,5-diaminoimidazoles (**41**) is the cyclization of various *N*-cyanomethylacetimidates by hydrazines (61JCS3816, 61JCS4845; 74BSF1453; 78JHC937).



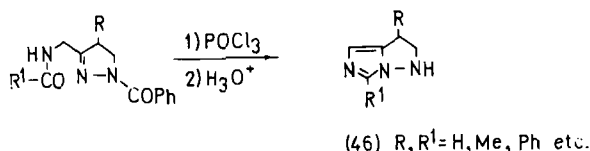
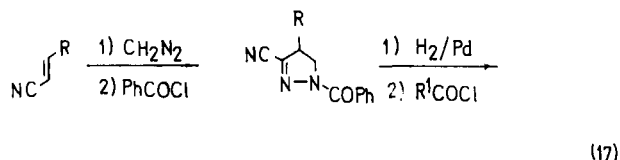
N-Aminoimidazoles **45** were obtained by recyclization of oxazole derivatives with hydrazine [Eq. (14)] (70GEP1923643) or recyclization of the readily available 2-amino-3-phenacyl-1,3,4-oxadiazolium salts (**42**) under the action of aqueous alkali (62ZC153; 64CB1031; 69ZC337), ammonia and alkyl amines (67CB3418; 70CB3533), amidines (70CB2845), ammonium hydrosulfide (65ZC378), and alkylmercaptans (70ZC289) [Eq. (15)]. Probably, in the latter method, salts **42** first are cyclized to imidazol[2,1-*b*]-1,3,4-oxadiazole derivatives (**43**); the oxadiazole ring then is opened on attack by a nucleophile. The formation of compounds **43** and their easy alkaline hydrolysis to 1-acylaminoimidazolinones **44** (Nu = OH) confirms this (70CB272). These conversions were summarized by Beyer (70ZC289).



Pyl *et al.* developed a two-stage synthesis of 1-aminoimidazoline-2-thiones from 2-amino-4-benzylthio-1,3,4-thiadiazole [Eq. (16)] (63LA113). This method is somewhat similar to the previous one and has preparative importance because of good yields.

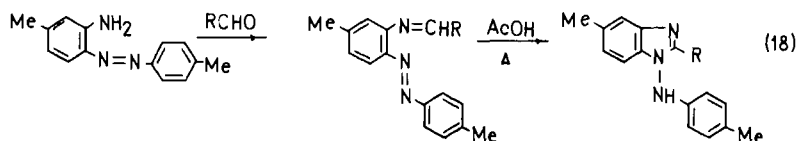


According to Eq. (17), a series of 2,3-dihydro-1*H*-imidazo[1,5-*b*]pyrrole derivatives (**46**) were obtained (78JOC4841). They were investigated as structural analogues of histamine.



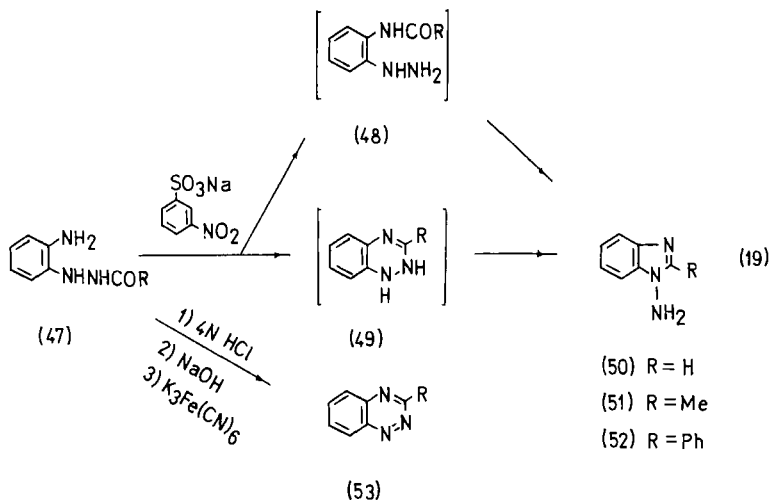
2. Benzimidazoles

The first representatives of *N*-aminobenzimidazoles described in the literature were 1-*p*-tolylamino-2-aryl-5-methylbenzimidazoles, which were obtained by Fischer from 2-amino-4,4'-dimethylazobenzene in accordance with Eq. (18) (22JPR102; 24JPR16).

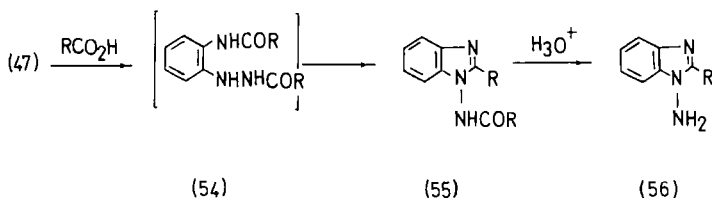


The parent of this series (**50**) and its derivatives (**51**) and (**52**) were obtained for the first time by Abramovitch and Schofield on heating acyl derivatives of *o*-aminophenylhydrazine (**47**) in aqueous solution of sodium *m*-nitrobenzenesulfonate [Eq. (19)] (55JCS2326). These authors assumed that in the course of the reaction, acylhydrazines **47** are rearranged to acylamino derivatives **48**, which are cyclized then to *N*-aminobenzimidazoles. However, on the basis of numerous data on rearrangement of dihydroazines into *N*-aminoazoles (cf., for instance sections II, F and II, I), one cannot exclude that the intermediate product of this reaction also may be 1,2-dihydrobenzo-1,2,4-triazine (**49**).

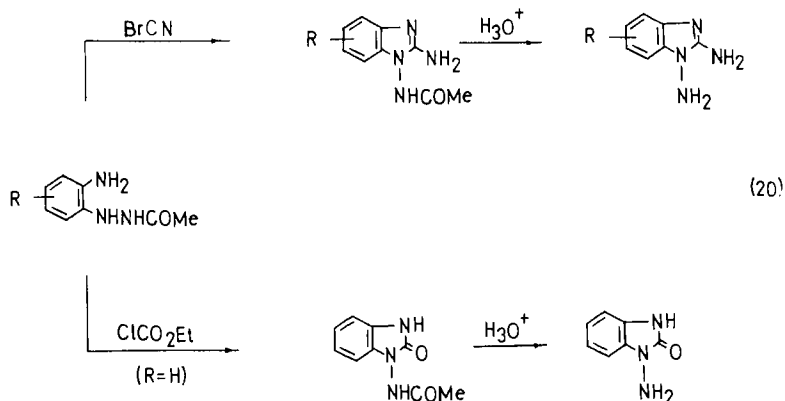
Abramovitch and Schofield established that the closure of the 1,2,4-triazine ring is really in competition with the formation of *N*-aminobenzim-



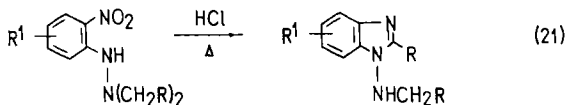
imidazoles, and if the reaction occurs in the presence of potassium ferricyanide, one can obtain the corresponding benzotriazine **53**, obviously, as a result of the oxidation of dihydro compound **49**. Checking these experiments, Sheng and Day could isolate only traces of amines **50–52**, and they also drew the conclusion that this is due to the strong competitive reaction leading to benzotriazines (63JOC736). This is why they modified the conditions of cyclization by heating compounds **47** with anhydrous carboxylic acid, the fragment of which should be placed in position 2 of the imidazole ring. By this method, 1-acylaminobenzimidazoles (**55**) were obtained in moderate or good yield and then produced amines **56**. Such conditions prevent benzotriazine ring closure, since the intermediate diacyl derivative **54** is able to be cyclized affording only *N*-aminobenzimidazole. This method was developed by Glover and co-workers [73JCS(PI)842].



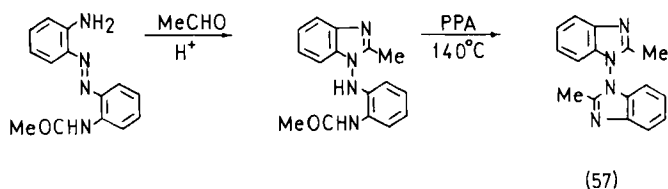
o-Aminophenylhydrazines were also used to obtain 1,2-diaminobenzimidazoles (73JOC3084; 77JOC542) and 1-aminobenzimidazolone (85JHC1089) [Eq. (20)].



Suschitzky and co-workers (73CC41) discovered that on refluxing *N*-alkylated *o*-nitrophenylhydrazines in hydrochloric acid, 1-alkylaminobenzimidazoles are formed in moderate yield [Eq. (21)]. In this rather complicated oxidation-reduction reaction, a positively charged chlorine ion or its equivalent is generated because, in some cases, the process is accompanied by electrophilic chlorination of the benzene nucleus.



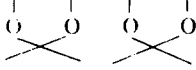
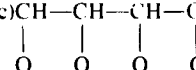
Spanish chemists were successful in the synthesis of 2,2'-dimethyl-1,1'-dibenzimidazolyl (**57**) from 2-amino-2'-acetaminoazobenzene [81JCS(P1)403]. This is the only known example of an *N,N'*-dibenzimidazolyl.¹



¹ *N,N'*-Dimers of noncondensed imidazoles are apparently unknown. Early reports (61AG808; 62BCJ2057; 63ZN406) of the formation of *N,N'*-dimers on oxidation of 2,4,5-triphenylimidazole with lead dioxide have not been confirmed. The two compounds formed in this reaction have been found to be 4,4'- and 1,2'-dimers (66JA3825).

At present, the main method for synthesizing *N*-aminobenzimidazoles is the direct amination of benzimidazoles (Table IV), first reported without experimental details in a German patent (73GEP2300521). Further investigations showed the best results were achieved by the use of a large excess

TABLE IV
N-AMINO BENZIMIDAZOLES OBTAINED BY DIRECT *N*-AMINATION

Substituents	Aminating agent	Yield %	Footnotes
None	HOSA	80	<i>a</i>
2-Me	HOSA	70	<i>b</i>
2-MeCHBu- <i>t</i>	MSH	13	<i>c</i>
2-CH(OH)Ph	HOSA	38	<i>c</i>
2-CH(OH)CH-CH-CH-CH ₂ 	HOSA	13	<i>c</i>
2-CH(OAc)CH-CH-CH-CH ₂ 	MSH	22	<i>c</i>
2-Ph	HOSA	22	<i>d</i>
2- <i>o</i> -ClC ₆ H ₄	HOSA	—	<i>e</i>
2- <i>o</i> -BrC ₆ H ₄	HOSA	—	<i>e</i>
2-(thiazolyl-4)-	HOSA	—	<i>e</i>
2-(thiazolyl-4)-5-NHCOPh	HOSA	—	<i>e</i>
2-(thiazolyl-4)-6-NHCOPh	HOSA	—	<i>e</i>
2-(thiazolyl-4)-5-NHCOOPr- <i>i</i>	HOSA	—	<i>e</i>
2-(thiazolyl-4)-6-NHCOOPr- <i>i</i>	HOSA	—	<i>e</i>
4,7-Me ₂	HOSA	60	<i>f</i>
5,6-Me ₂	HOSA	70	<i>g</i>
2-NH ₂	HOSA	49	<i>h</i>
2-NH ₂	HOSA	86	<i>i</i>
2-NH ₂	DNPH	35	<i>h</i>
2-NH ₂ -5,6-Me ₂	HOSA	25	<i>h</i>
2-NHCOOMe	HOSA	—	<i>e</i>
2-Cl	HOSA	24	<i>a</i>
2-SO ₃ H	HOSA	73	<i>j</i>

^a (89KGS221)

^b (80KGS814)

^c [87JCS(P1)2787]

^d (89KGS1486)

^e (73GEP2300521)

^f (83KGS386)

^g (81KGS1497)

^h (77JOC542)

ⁱ (89KGS209)

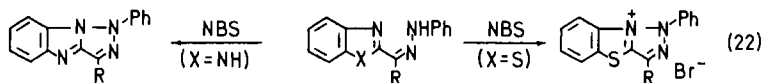
^j (88KGS1070)

of HOSA as the aminating agent in aqueous alkaline solution. For example, the yield of 1-aminobenzimidazole **50** is increased to 80% (89KGS221). The reports of poor yields (13–20%) are due to the use of an unsuitable solvent (78CPB2522) or to an insufficient excess of HOSA [80JCR(M)514].

If a bulky substituent is in position 2 of the imidazole ring, the yield of the product aminated by HOSA is sharply decreased, and in such cases the use of MSH is more preferable [86CC832; 87JCS(P1)2787]. The latter reagent is usually applied to obtain 1-R-aminobenzimidazolium salts by amination of various 1-R-benzimidazoles [73CI(L)952; 76JCS(P1)367; 79CPB2521; 88JCS(P1)3381]. The other method to synthesize such salts is the alkylation of 1-aminobenzimidazoles (Section IV,C,1).

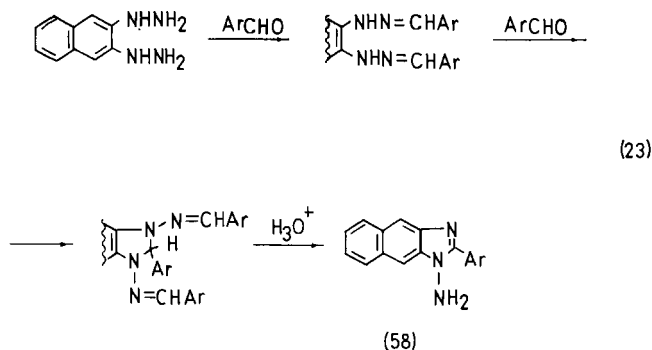
Many 1-amino-2-R-benzimidazoles, which are otherwise difficult to synthesize, can be obtained by nucleophilic substitution of the sulfo group in 1-amino-2-benzimidazosulfonic acid (cf. Section IV,F). All attempts to synthesize 1-aminobenzimidazoles by reduction of 1-nitrosobenzimidazoles failed (53CB1101; 63JOC736).

As a specific kind of intramolecular amination, one can consider the oxidative cyclization of arylhydrazones of benzazolyl-2-ketones by the action of *N*-bromosuccinimide (67AG272) [Eq. (22)]. This reaction occurs most easily for hydrazones of benzimidazoles, and this process is more difficult in the case of benzothiazoles; weakly basic hydrazones of benzoxazolyl-2-ketones do not take part in this conversion.

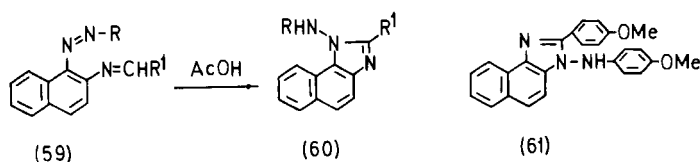


3. Other Imidazole Systems

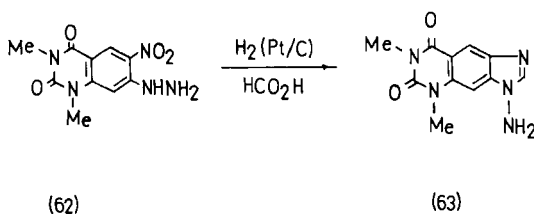
At the beginning of this century Franzen worked out an original method for synthesizing 1-amino-2-arylnaphtho[2,3-*d*]imidazoles (**58**) starting from 2,3-dihydrazinonaphthalene [Eq. (23)] [06JPR545; 08JPR(77)193]. He investigated many general reactions of amines **58**, such as deamination by nitrous acid, formation of Schiff bases, acylation, addition of phenyl isocyanate, quaternization of the 3-N atom, and others. By these reactions the structure of **58** was corroborated. In addition to their experimental importance, these results have historical interest, since they were far ahead of investigations on other condensed *N*-aminoimidazoles.



Fisher synthesized a large group of 1-arylamino-2-arylnaphtho[1,2-*d*]imidazoles (**60**) by cyclization of 1-benzeneazo-2-arylideneaminonaphthalenes under acidic conditions (22JPR102; 24JPR16). It was shown later that this reaction can occur on heating **59** in pyridine (67AG(E)250). 3-Arylamino derivatives of naphtho[1,2-*d*]imidazole (**61**) were obtained by this method.

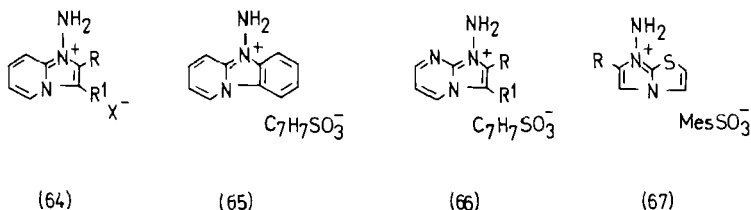


8-Amino-1,3-dimethylimidazo[4,5-*g*]quinoxaline-2,4-dione (**63**) was obtained in 54% yield by the reductive cyclization of nitrohydrazine **62** (84JHC791).

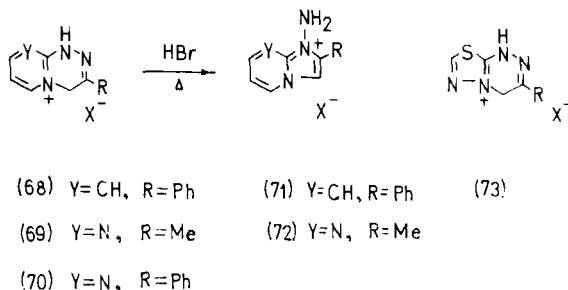


Amination of the corresponding bridge nitrogen heterocycles produces salts of 1-aminoimidazo[1,2-*a*]pyridinium (**64**) [71JCS(C)3280], 5-aminopyrido[1,2-*a*]benzimidazolium (**65**) [76JCS(P1)367], 1-aminoimidazo[1,2-*a*]pyrimidinium (**66**) [77JCS(P1)78], and 7-aminoimidazo[2,1-*b*]thiazolium (**67**) [74JCS(P1)1137]. The aminating agents were TSH and

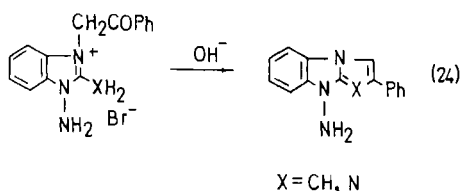
MSH. Only for the synthesis of salt **64** ($R = R' = H$), was HOSA used; however, the yield was about 15% [71JCS(C)3280]. A large series of salts of type **64** was obtained by acidic cyclization of 1-acylmethyl-2-(2-acetylhydrazino)pyridinium salts [71JCS(C)3280].

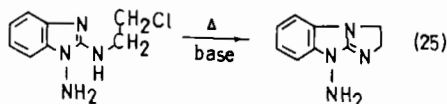


Bradsher and co-workers discovered that 1-amino-2-phenylimidazo[1,2-*a*]pyridinium salts (**71**) can be obtained in 68% yield on long-term refluxing of dihydrotriazinium salts **68** in hydrobromic acid (69JOC2129). Later, this reaction was extended to the synthesis of 1-amino-2-methylimidazo[1,2-*a*]pyrimidinium salts (**72**) from **69**. It was found impossible to carry out such a ring contraction in the 3-phenyl derivative (**70**) or in 1,4-dihydrothiadiazolo[2,3-*c*]-1,2,4-triazinium salts (**73**) [74JCS(P1)1137].

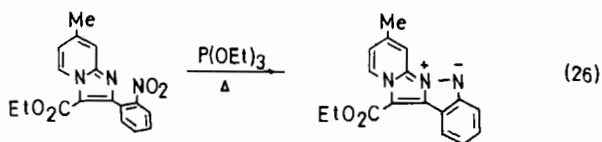


Syntheses of condensed *N*-aminoimidazoles can also occur by building new rings onto *N*-aminoimidazole as shown by Eq. (24) (79MI1; 90KGS1689) and Eq. (25) (88KGS1070).





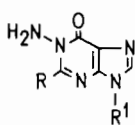
An example of an intramolecular amination of condensed imidazoles via nitrene was described [89JCS(P1)961] [Eq. (26)].



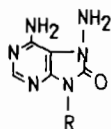
D. N-AMINOPURINES

Numerous representatives of all possible types of *N*-aminopurines, namely, 1-, 3-, 7-, and 9-aminopurines are known. We first examine their syntheses by direct N-amination.

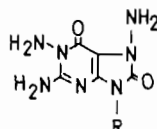
Broom and Robins were the first to carry out the direct N-amination of purines by the action of HOSA on inosine, guanosine and 2'-deoxyguanosine in aqueous alkaline solutions, affording 1-aminoderivatives **74** in 33–65% yield (69JOC1025). Amination of 8-oxo-adenosine and 1-amino-8-oxoguanosine gave rise to 7-amino-substituted compounds **75** and **76** ($R = \beta$ -D-ribofuranosyl). Japanese chemists verified these data and determined in addition that at pH 2–4, guanosine is aminated on the carbon atom yielding 8-aminoguanosine (72CPB2073).



(74)



(75)



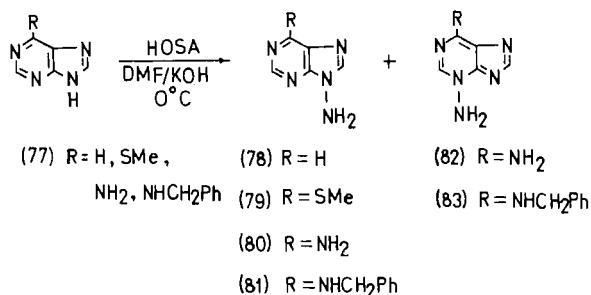
(76)

$R=H$, $R^1=\beta$ -D-ribofuranosyl

$R=NH_2$, $R^1=\beta$ -D-ribofuranosyl

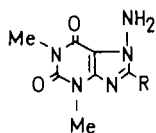
$R=NH_2$, $R^1=2$ -deoxy- β -D-ribofuranosyl

Amination of purine itself and some of its simple derivatives (**77**) by HOSA in DMF-KOH medium was investigated by Somei *et al.* (78CPB2522). They found that under these conditions, purine and 6-methylthiopurine are aminated only at position 9, and the yield of amines **78** and **79** are 6–11%, even in the presence of a large excess of HOSA. On amination of adenine together with 6,9-diaminopurine **80** (5% yield), the formation of a small amount (0.5%) of 3,6-diaminopurine **82** was noted. The amination of position 3 is manifested for 6-benzylaminopurine; the yield of compounds **81** and **83** is 25% and 5%, respectively.



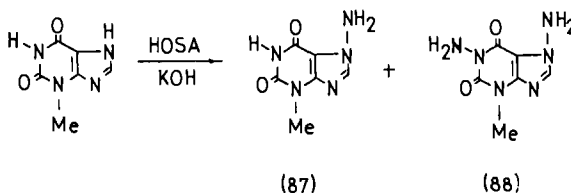
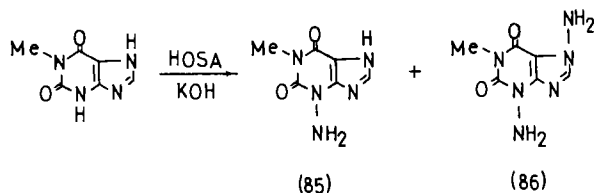
9-Benzylhypoxanthine is aminated by HOSA in alkaline media at position 1 (85JHC753). Under neutral conditions, adenine and its 7- and 9-substituted derivatives are aminated by MSH, affording 1,6-diaminopurinium salts (74JOC3438; 85RTC302).

The amination of xanthines was investigated in more detail. Theophylline (81MI1; 82S592; 83KGS1564; 87KGS1555) and its 8-methyl, 8-amino, and 8-halogeno derivatives (83KGS1564; 87CPB4031, 87KGS1398, 87KGS1555) are aminated only at position 7, resulting in good (R = H, NH₂) or moderate (R = Me, Cl, Br) yields of amines **84**. Under the same conditions, the present authors failed to aminate 8-nitro- and 8-phenyltheophylline, probably because of steric hindrance and decreased nucleophilicity of the N-anion.



(84) R = H, Me, Br, Cl, NH₂

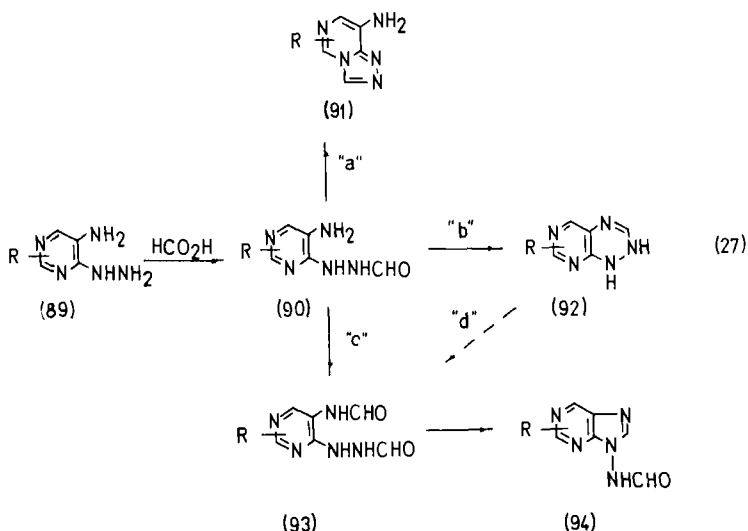
1-Methylxanthine is aminated by HOSA in aqueous alkali affording a mixture of 3-amino- (**85**) and 3,7-diamino derivatives (**86**) in yields of 55% and 10%, respectively (90ZOR1322). Under the same conditions, 3-methylxanthine gives a mixture of monoamine **87** and diamine **88** in yields of 67% and 7%, respectively (88ZOR1524). In both cases, the mono- and diamines are easily separated.



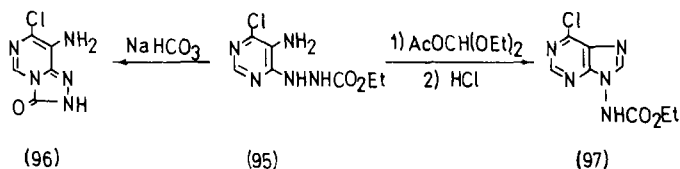
3,7-Dimethylxanthine (theobromine) as the sodium salt is smoothly aminated by DPPH (82S592) or HOSA (81MI1) affording the 1-aminoderivative in good yield. There is no information about N-amination of xanthine itself.

The most general and probably the best method for synthesizing 9-aminopurines makes use of the cyclization of suitable 5-amino-6-hydrazinopyrimidines. As cyclizing agents, formic acid or ortho-formates are often used; the best mixture is of *ortho*-formate and acetic anhydride. The cyclization process is often accompanied by side reactions [Eq. (27)].

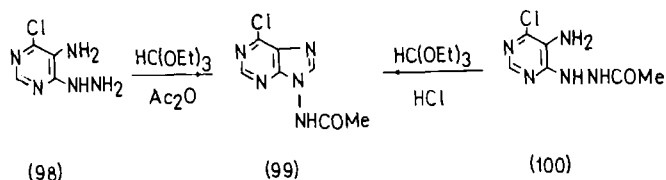
The hydrazino group in **89** is more nucleophilic than the 5-amino group, therefore, formylhydrazino derivative **90** is usually formed at the first stage. This compound, depending on conditions and on the type of cyclizing agent, can be converted then to triazolo[4,3-*c*]pyrimidine **91** [pathway a in Eq. (27)], 1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (**92**) (pathway b), or diformyl derivative (**93**) (pathway c). Compound **93** is the precursor of 9-acylaminopurine (**94**). There is also much evidence of the formation of 9-acylaminopurines via dihydroazines (**92**) (pathway d).



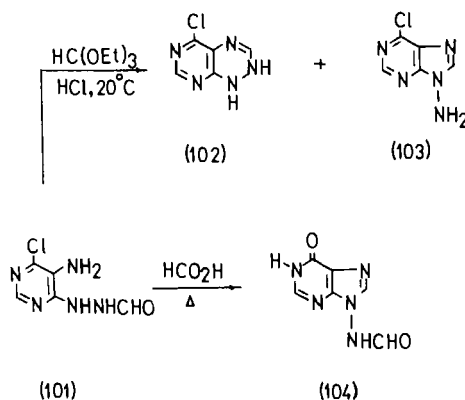
Alkaline conditions favor the formation of triazolo[4,3-*c*]pyrimidines (**91**). Thus, on heating in an aqueous solution of NaHCO_3 , 4-chloro-5-amino-6-(ethoxycarbonyl)hydrazinopyrimidine (**95**) is converted to triazole **96**. The action of diethoxymethylacetate on **95**, followed by heating in hydrochloric acid, gives 9-aminopurine **97** (63JOC2257).



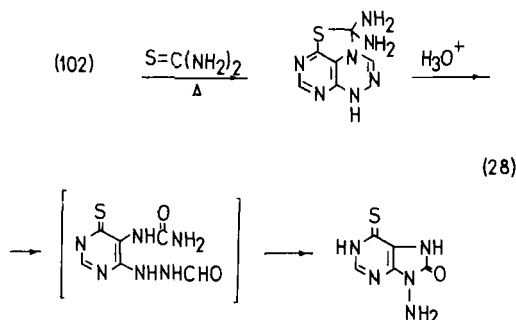
Montgomery *et al.* obtained 6-chloro-9-acetamidopurine (**99**) by the action of a mixture of *ortho*-formate and acetic anhydride on aminohydrazine **98** (60JA4592). The same compound is formed on heating 4-chloro-5-amino-6-acetylhydrazinopyrimidine (**100**) with *ortho*-formate in the presence of hydrochloric acid (63JOC923).

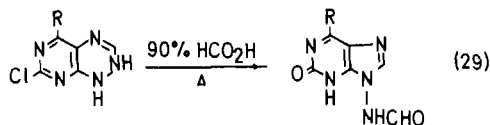


In contrast to **100**, its formyl analogue **101** does not give a definite purine compound under the same conditions. However, on treatment of **101** with *ortho*-formate in the presence of a small amount of HCl, a mixture of dihydrotriazine **102** (57%) and 6-chloro-9-aminopurine (**103**) (13%) was obtained. Refluxing of **101** in formic acid leads to 9-formamidohypoxanthine (**104**). The latter reaction occurs via the intermediate formation of dihydrotriazine **102**, i.e., the process proceeds according to pathway d in Eq. (27) and is accompanied by hydrolysis of a C—Cl bond (63JOC923). 9-Acetamidohypoxanthine was synthesized by the reductive cyclization of 5-nitro-6-formylhydrazinopyrimidine-4-one by Na₂S₂O₄ in acetic acid (69JOC2102).



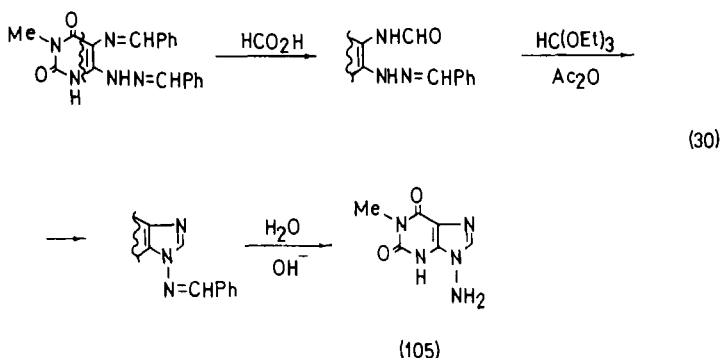
Additional data on ring contractions in 1,2-dihydropyrimidotriazines were obtained by Temple *et al.* (69JOC3161) [Eq. (28)] and by Brown and Sugimoto [71JCS(C)2616] [Eq. (29)].



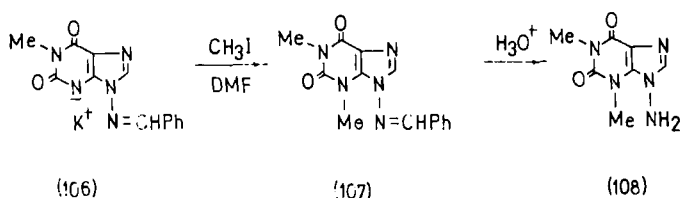


The synthesis of unsubstituted 9-aminopurine (60JA4592) and its 2,6-dimethyl derivative [70JCS(C)139] from the corresponding 5-amino-4-hydrazinopyrimidine and formic acid or *ortho*-formate in the presence of HCl was reported.

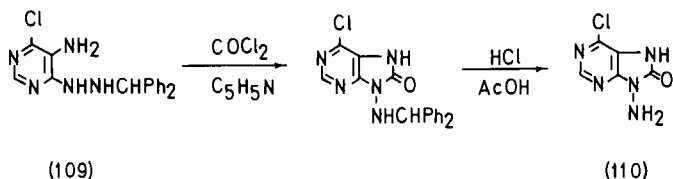
One of the best modifications for synthesizing 9-aminopurines is to use benzylidene hydrazones of 5-amino-4-hydrazinopyrimidines as the starting materials. The benzylidene group blocks the N-2 atom in the hydrazino group and prevents the undesirable cyclizations to triazole **91** or dihydrotriazine **92** [Eq. (27)]. This method was used to obtain 9-aminohypoxanthine (60JA4592) and 9-benzylideneamino-6-methylthio-8-R-purines (R = H, Me) (61JOC4961). This gave especially good results in the synthesis of 9-amino-1-methylxanthine [**105**, Eq. (30)] (87KGS836).



It was not possible to obtain 9-aminotheophylline (**108**) by this pathway or by alkylation of the potassium salt of (**105**). However, **108** can easily be synthesized by methylation of the potassium salt of 1-methyl-9-benzylideneaminoxanthine (**106**) followed by hydrolysis of the Schiff base **107**.



In one case, the benzhydryl group was used to protect the hydrazino function in 5-amino-6-hydrazinopyrimidine (**109**) (68JOC530). If the unsubstituted aminohydrazine is taken instead of **109**, purine **110** is not formed, as was mistakenly reported (63JOC2677). The corresponding triazolone is formed, however.

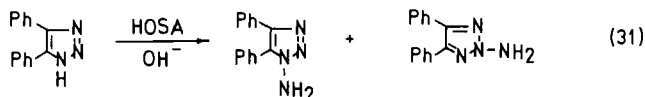


In the final stage of purine biosynthesis, the closure of the pyrimidine ring takes place in the corresponding 1-R-5-amino-4-carboxamidoimidazole. This approach is often used in the laboratory as well. Thus, it was a means of obtaining 9-aminopurines from compounds of type **41** ($\text{R}^2 = \text{CONH}_2$) (61JCS3818; 61JCS4845) and 1-aminopurines from 4-amino-5-imidazolocarboxylic acid hydrazide (85JHC753, 85JHC1435). The synthesis of 1-aminoxanthine by recyclization of xanthines by the action of hydrazine (69JOC2157; 82H2291; 85YZ730) has been described.

E. N-AMINO-1,2,3-TRIAZOLES

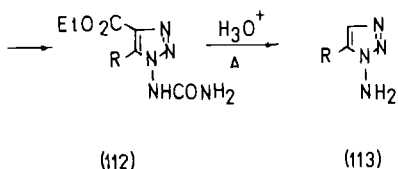
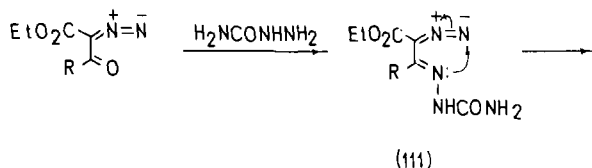
1. Noncondensed 1,2,3-Triazoles

1- and 2-isomers of *N*-amino-1,2,3-triazoles exist. Information about 2-amino-*v*-triazoles is found in only two reports describing the amination of 4,5-diphenyl-*v*-triazole by the use of chloroamine (67TH1) and HOSA [Eq. (31)] (88M1041). In the latter case, a mixture of 1- and 2-aminotriazoles was obtained in a total yield of 94%; the mixture was separated by chromatography. The ratio of the isomeric amines was about 1 : 1.

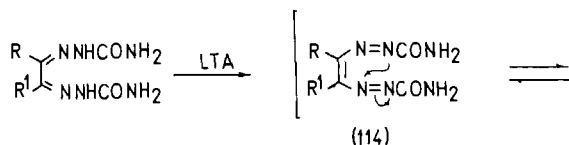


All other papers are concerned with the more accessible 1-aminotriazoles. Pechmann (1900CB644) and Wolff (02LA125; 03CB3617) first independently synthesized these compounds. However, in contrast to Wolff, Pechmann made a mistake in the correct choice of a structure of the

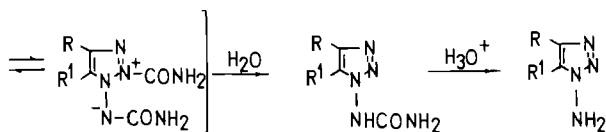
products (see later). Wolff carried out the reaction of α -diazoketones with semicarbazide. The semicarbazone **111** thus formed is cyclized at once to ureidotriazole **112**, and hydrolysis and decarboxylation of the latter compound led to 5-substituted 1-aminotriazoles (**113**).



This method was substantially modified latter by Alexandrou and Adamopoulos, who oxidized bissemicarbazones of α -dicarbonyl compounds with lead tetraacetate [Eq. (32)] (76S482). Supposedly, the oxidant is necessary for conversion of bissemicarbazone to bisazo-compound (**114**), which is transformed to 1-ureidotriazole via triazole betaine (**115**). If substituents R and R' differ, a mixture of two isomeric 1-aminotriazoles is formed, and the isomer with a bulky substituent in position 4 predominates.

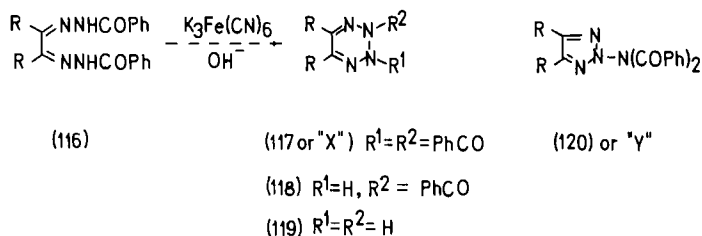


(32)



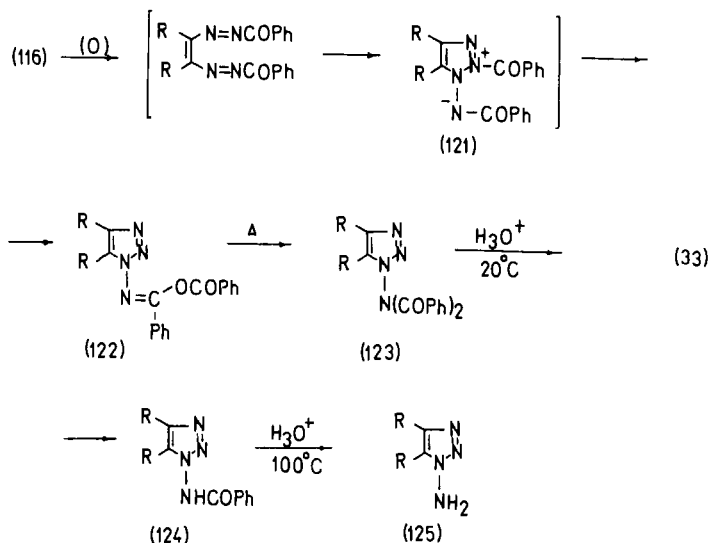
(115)

The oxidation of bishydrazones to synthesize 1-amino-1,2,3-triazoles was investigated first by Pechmann (1900CB644; 09CB659) and Stolle [03JPR469; 04JPR433; 08JPR(78)544]. They treated benzyl, diacetyl, and glyoxal bisbenzoylhydrazones (**116**) with potassium ferricyanide and other oxidants and isolated products described at first as 2,3-dibenzoyl-2,3-dihydro-1,2,3,4-tetrazines (**117**). The products of their hydrolysis were described as structures **118** and **119**. Moreover, it was noted that the primary product (let us call it X), having the proposed structure **117**, is isomerized on heating to another substance, Y, which is transformed on hydrolysis also to **118** and **119**. In 1908, Stolle also made a mistaken (although closer to a true) proposal that the product, Y, has a structure of 2-dibenzoylamino-1,2,3-triazole (**120**). Stolle proposed this because, on hydrolysis, Y followed by deamination of the resultant amine with nitrous acid gives the known 1,2,3-triazole derivatives [08JPR(78)544]. Only in 1926 did Stolle at last reach the correct conclusion that Y is 1-dibenzoylamino-1,2,3-triazole (**123**), and the products of its hydrolysis have the structures **124** and **125** (26CB1743).



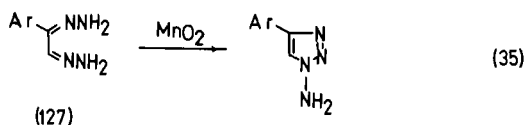
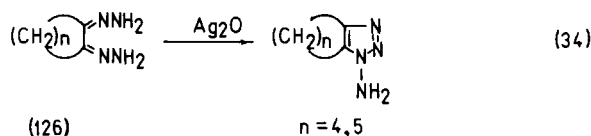
It should be emphasized that the dihydrotetrazine structure (**117**) proposed for the primary oxidation product, X, was still accepted during the 1960s and 1970s, when it became a subject for contradictory conclusions and intensive investigations. As alternatives, the betaine structure **121** (70AG81) and so-called triazolyl-isoimide **122** (63T1697; 66T1309) were proposed. The latter proposal was correct, as was proved by X-ray analysis [72JCS(P2)662]. Isoimides **122** were also obtained by an independent route (78JHC1255; 84JHC1653). Thus, the definitive version of Pechmann's synthesis of 1-amino-*v*-triazoles now can be presented by Eq. (33).

Greek chemists investigated the mechanism of oxidation of bisaroylhydrazones of α -dicarbonyl compounds (66T1309; 72JOC2345), the kinetics of isomerization of isoimides (77JHC269; 78JHC1255; 84JHC1653), and the dipole moments and conformations of isoimides [77JCS(P2)1779; 79JHC571] and 1-diaroylamino-1,2,3-triazoles (83JHC1469). With an ortho-

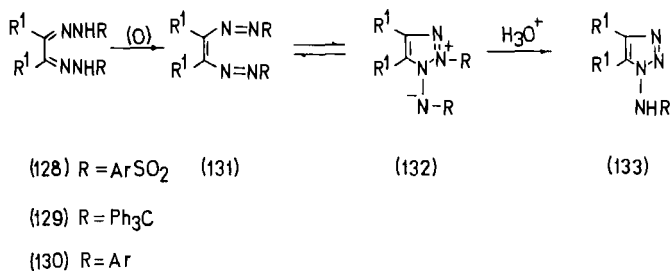


substituent in the aryl nucleus of bisaroylhydrazones, the oxidation leads at once to formation of 1-arylamino-1,2,3-triazoles (124) (66T1309; 72JOC2345). The same occurs on oxidation of bisarylacetylhydrazones of α -dicarbonyl compounds (79JHC1373). On oxidation of bisacetylhydrazones, isoimides of type 122 are formed in poor yield, and the total process is complex (72JOC2345). The data obtained were interpreted to favor the formation of bisazo compounds in the first step, and these compounds are then cyclized to betaine 121, which are easily isomerized to isoimides. As shown here, betaines of type 121 can be isolated in some cases.

Bishydrazones 126 and 127, unsubstituted at the nitrogen atoms, on oxidation immediately form 1-amino-1,2,3-triazoles in 20–60% yields [Eqs. (34) and (35)] (61CB3260; 71JPR882). For 127, the reaction is sensitive to steric hindrance, and the formation only of 1-amino-4-aryltriazoles is the evidence for this.

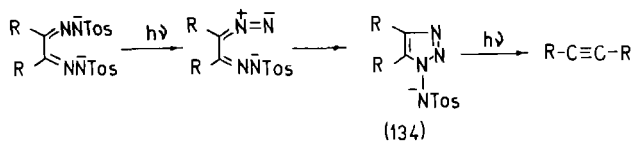


Bisarylsulfonyl- (**128**) [72JCS(P2)662], bistrisphenylmethyl- (**129**) (62JOC4300), and bisaryl-hydrazones (**130**) [71TL633; 72T3987; 89JCS(P1)159] of α -dicarbonyl compounds form, on cautious oxidation with I_2 , $K_3Fe(CN)_6$, Ag_2O , or others in alkaline medium, the red, rather unstable bisazocompounds **131**. The latter, on treatment with acids, are rapidly cyclized to 1-aminotriazoles **133**. Bisarylsulfonylhydrazones **128** can be converted directly to **133** on oxidation by lead tetraacetate (LTA) or mercuric diacetate [78JCS(P1)881]. Perhaps the bisazo compounds are in tautomeric equilibrium with triazole betaines (**132**), which can be captured by various 1,3-dipolarophiles (cf. section IV,E,7).



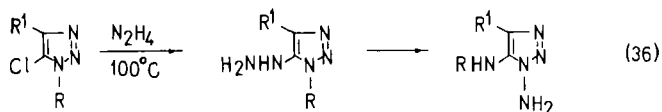
Another bishydrazone route involves heating bisarylsulfonylhydrazones of α -dicarbonyl compounds (**128**) with alkali in ethylene glycol to give 4,5-dimethyl-, 4,5-dipropyl-, and 4,5-diphenyl-1-tosylamino-triazoles [52JCS4735; 72JCS(P2)662; 73JCS(P1)555]. The bistosylhydrazone of 1-phenylpropane-1,2-dione yields a mixture of 4-phenyl-5-methyl- and 4-methyl-5-phenyl-1-tosylaminotriazole in a ratio of 13 : 5 [73JCS(P1)555]. Bisarylsulfonylhydrazones of cyclohexane-1,2-diones are converted to the corresponding 1-arylsulfonylaminotriazoles under acidic as well as alkaline conditions (89JHC301).

Photolysis of bistosylhydrazone dianions, depending on the wavelength of irradiation, can be directed to form 1-tosylaminotriazole or the corresponding acetylene, the latter by fragmentation of the anion **134** (64AG144; 69JOC1746).



Recently, the Belgian chemists suggested a novel method to synthesize 1-amino-1,2,3-triazoles with the use of recyclization of 1-aryl-5-chlorotri-

azoles (89BSB343) and 5-chloro-1,2,3-thiadiazoles (89JHC1811) under the action of hydrazine. 5-Hydrazinotriazoles are intermediates in this conversion [Eq. (36)].

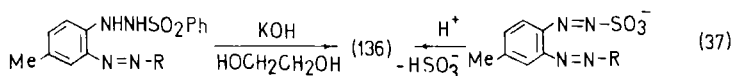
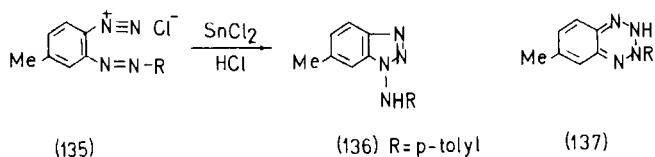


2. Benzotriazoles

There are two general approaches to synthesize *N*-aminobenzotriazoles:

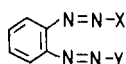
- (1) Direct amination of benzotriazoles
- (2) Cyclization of various 1,2-diazobenzenes, in particular, 2-hydrazinobenzenediazonium salts.

The second approach, resembling the synthesis of 1-amino-*v*-triazoles from bishydrazones of α -dicarbonyl compounds, has a long history and is more general for 1-aminobenzotriazoles, but is not applicable to 2-aminobenzotriazoles. This method was first carried out by Zincke and co-workers (1886CB1452; 1887CB2896). They reduced the diazonium salt **135** by tin dichloride and isolated a product mistakenly described as dihydrobenzotriazine **137**. Later, this structure was repeatedly corrected, but only in 1964 did Katritzky and co-workers finally establish that the compound is 1-*p*-tolylamino-6-methylbenzotriazole (**136**) (64JCS4394). In addition to physical methods for the structural proof of **136**, the independent synthesis of this compound was carried out as shown in Eq. (37).

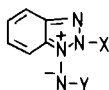


Various modifications of the Zincke method were used to obtain perfluoro derivatives of 1-anilinobenzotriazole [70JCS(C)1519], namely 1,1'-dibenzotriazolyl (65USP3184472) and 1,2'-dibenzotriazolyl (65USP3184471).

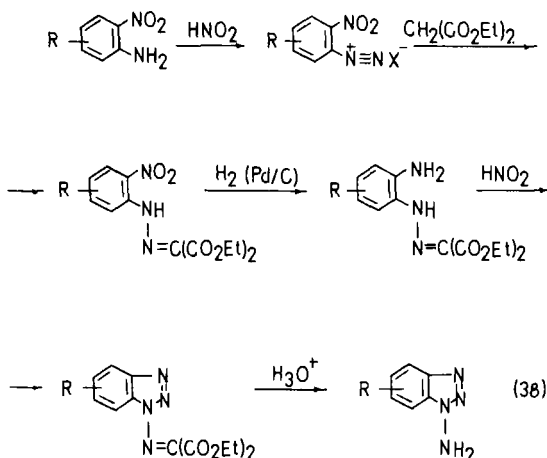
Katritzky and co-workers investigated the cyclization parameters for *ortho*-diazo compounds in the benzene series (64JCS751) and determined that if substituents X and Y are aryls, the compounds exist as the ring-open form **138**. If one of the substituents is electron withdrawing, for instance, CN or PhSO₂, the 1-aminobenzotriazole structure **139** is favored.



(138) X=Y=Ar

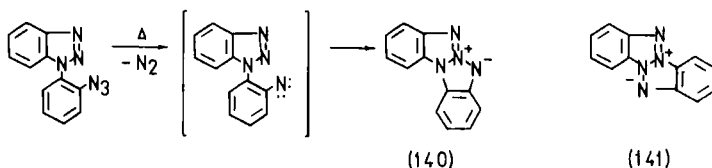
(139) X=Ar, Y=CN, PhSO₂

Italian chemists worked out an important modification of the Zincke method, allowing the synthesis of 1-aminobenzotriazoles having the substituted amino group (60MI1) to be achieved. The method includes the formation of an *o*-aminoarylhydrazine where the hydrazino group is protected using an active methylene compound, for instance, malonic or cyanoacetic ester. This allows for ready triazole ring closure, affording the Schiff base; the latter compound then is hydrolyzed to the corresponding 1-aminobenzotriazole [Eq. (38)]. This method has been improved [69JCS(C)742; 70JCS(C)583].



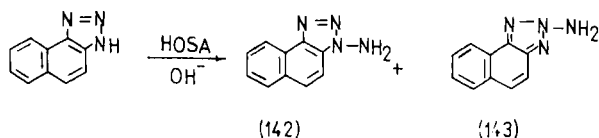
The direct amination of benzotriazole by the use of HOSA was first reported in a patent (65USP3184471). The total yield of 1- and 2-amino-benzotriazoles, separated by crystallization, was not high (20%). Later, Rees and co-workers changes the conditions of amination and achieved yields of 38% and 11% for 1- and 2-amino derivatives, respectively [69JCS(C)742]. Amination of the sodium salt of benzotriazole with chloroamine failed. An attempt to exchange the chlorine atom for the amino group in 1-chlorobenzotriazole under the action of sodium amide was also unsuccessful [69JCS(C)1474].

On intramolecular nitrene amination, mesoionic compounds **140** and **141** were obtained (69JA2453; 65JCS4831).



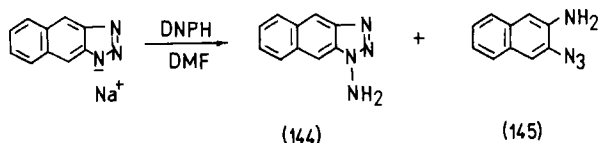
3. Other Condensed 1,2,3-Triazoles

Most of the isomeric *N*-aminonaphthotriazoles have been described. Direct amination of naphtho[1,2-*d*]triazole gives its 3-amino (**142**) and 2-amino (**143**) derivatives in yields of 24% and 23%, respectively [67JCS(C)1276]. However, on repeating the experiment, the yield of amines was worse (18% and 3%, respectively) [69JCS(C)756]. Traces of the uncharacterized 1-amino derivatives were found in the mixture. 3-Aminonaphtho[1,2-*d*]triazole was also obtained in several steps from 2-amino-1-nitronaphthalene [67JCS(C)1276].

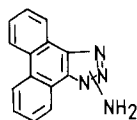
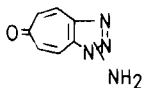
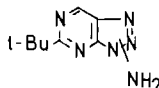
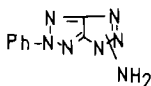


On amination of naphtho[2,3-*d*]triazole, amine **144** is formed; however, information about its yield is contradictory: 62% [67JCS(C)1276] and 27% [69JCS(C)756]. 2-Amino-3-azidonaphthalene (**145**) was also isolated from the mixture in a yield of 2%. It was assumed that the latter compound is

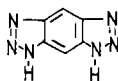
formed from 2-aminonaphtho[2,3-*d*]triazole on isomerization in alkaline medium.



Amination of the sodium salt of phenanthro[9,10-*d*]triazole with the use of *O*-(2,4-dinitrophenyl)hydroxylamine in DMF leads to the formation of 1-amino (146) and 2-amino (147) derivatives in 33% and 13% yields, respectively. With HOSA, the yield was considerably smaller [72JCS(P1)634]. Amination of the sodium salt of the corresponding triazoles by the action of DNPH or MSH produced *N*-aminotriazoles 148 and 149 (75AG742), 150–152 (87JHC705), and 153 (88CC1608). The amination of benzo[1,2-*d* : 4,5-*d'*]bistriazole (154) by HOSA or DNPH gives rise to the complex mixture of mono- and diamines separated by fractional crystallization (86JOC979).

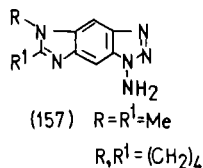
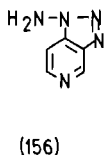
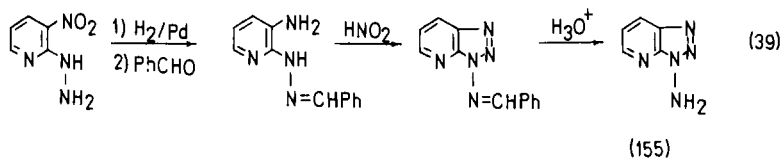
(146) 1-NH₂ (33%)(148) 1-NH₂ (47%)(150) 1-NH₂ (10–31%)(147) 2-NH₂ (13%)(149) 2-NH₂ (28%)(151) 2-NH₂ (5%)(152) 3-NH₂ (26–50%)

(153)



(154)

3-Aminotriazolo[4,5-*b*]pyridine (155) has been synthesized [69JCS(C) 1758] starting from 2-hydrazino-3-nitropyridine, [Eq. (39)], a route which is similar to the Italian method in Eq. (38). In the same way, amine 156 was obtained as well as the quinoline analogues of compounds 155 and 156. The Italian method [Eq. (38)] was used to obtain *N*-aminotriazole 157 from 5-amino-6-nitrobenzimidazoles (70CC1458).



F. *N*-AMINO-1,2,4-TRIAZOLES

The numerous *N*-amino-1,2,4-triazoles described at the present time can be divided conveniently into five large groups:

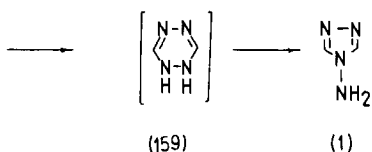
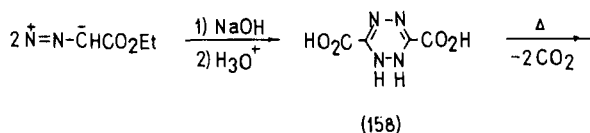
- (1) Unsubstituted *N*-amines and their derivatives having the *C*-alkyl and *C*-aryl substituents
- (2) *N*-Aminotriazoles with amino groups in positions 3 and 5
- (3) Oxygen-containing *N*-aminotriazoles
- (4) Sulfur-containing *N*-aminotriazoles
- (5) *N*-Amino derivatives of the condensed 1,2,4-triazoles.

1. 1,2,4-Triazole and Its *C*-Alkyl and *C*-Aryl Derivatives

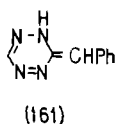
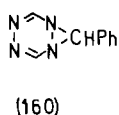
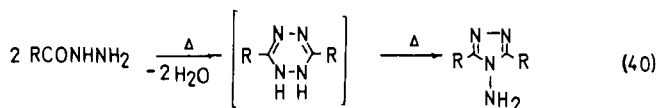
From the very beginning, the chemistry of *N*-amino-*s*-triazoles was tightly interlaced with the chemistry of the isomeric *s*-dihydrotriazines. A typical example is found in the history of the synthesis of the series parent—4-amino-*s*-triazole (1). Probably, this compound was first obtained by Curtius and Lang (1888JPR531). They, and a little later Hantsch and co-workers (1900CB58), investigated dimerization of diazoacetic ester in an alkaline medium and isolated the disodium salt of 1,2-dihydro-*s*-tetrazine-3,6-dicarboxylic acid, and then acid **158**. On thermolysis or on heating in acidic medium, this acid was transformed to the compound which was described as 1,2-dihydrotetrazine **159**, in spite of its conversion into the known 1,2,4-triazole by the action of nitrous acid.

Only in 1906–1907, did Bülow and also Curtius and co-workers revise the dihydrotetrazine structure and make a final choice in favor of 4-amino-

s-triazole (**1**). In particular, Bülow demonstrated the ready reaction of **1**, as is characteristic for most primary amines, with 1,4-dicarbonyl compounds (acetonylacetone, diethyl succinate, etc.), affording the corresponding pyrrole derivatives (cf. Section IV,C,4) (06CB2618, 06CB4106). Curtius and co-workers, on reduction of *s*-tetrazine, obtained authentic 1,2-dihydro-*s*-tetrazine and discovered that on heating above 130°C, the latter compound is isomerized to the earlier obtained product, i.e. 4-amino-*s*-triazole (**1**) (07CB815).

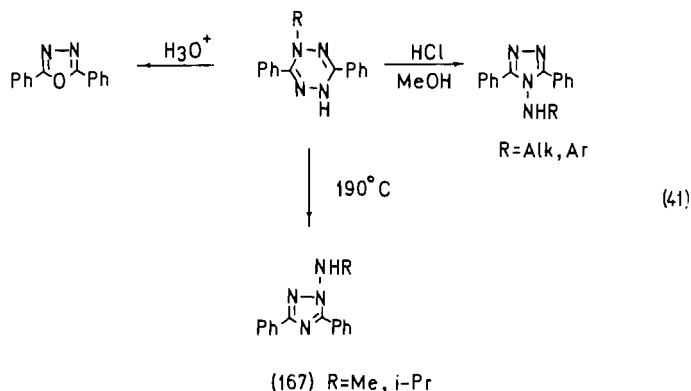


Almost simultaneously, several teams of chemists worked out another method of synthesizing the supposed 1,2-dihydro-*s*-tetrazines by heating *N*-acyl- and *N,N'*-diacylhydrazines at temperatures of 150–200°C (1896G430; 1899JCS1132; 1899MI1; 03JPR464; 05JCS1768). Taking into account the elevated temperature of the reaction, undoubtedly, *N*-amino-triazoles [Eq. (40)], but not dihydro-*s*-tetrazines were the result of most of these experiments. Deamination of the products to triazoles under the



and its course can be changed depending on conditions. Thus, 1,2-dihydro-tetrazines, obtained on interaction of the amidinium salts with hydrazine, are converted into *N,N'*-diacyl hydrazines (**165**) on heating with aqueous acids. Only in methanolic hydrogen chloride solution at 0–5°C is isomerization of 1,2-dihydrotetrazines to 4-aminotriazoles (**166**) observed [73JCS (P1)335].

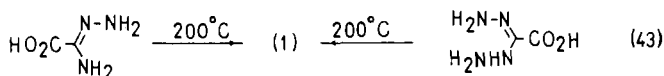
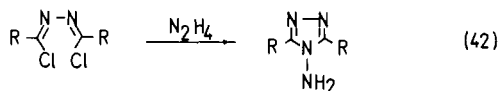
Acidic hydrolysis and thermolysis of 1,4-dihydrotetrazines can also occur in several ways [Eq. (41)] [84JCS(P1)2779]. It should be noted that thermolysis in this case yields the less accessible 1-alkylamino-*s*-triazoles (**167**).



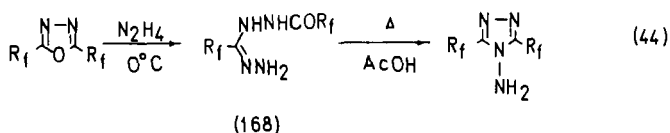
The simplest method to synthesize 4-amino-*s*-triazole and some of its 3,5-dialkyl and diaryl derivatives is the reaction of hydrazine hydrate with carboxylic acids (11G20; 11G93; 44OS12; 53JOC872; 53MI1; 58ZOB2773), their esters (05JCS1768), ortho-esters (03JPR464; 17JPR312), and hydrazides (09G535; 69KGS157). The heterocyclization process occurs via the corresponding mono- and diacylhydrazines, which can be isolated and separately cyclized on heating at 150–200°C or in the presence of various condensing agents (03JPR464; 14JPR508).

Instead of carboxylic acids, nitriles [1894CB3273, 1894JPR241; 21JPR113; 56JCS2253; 60M294, 60M595; 64CB523, 64CR1262; 72JCS (P1)2395], iminoesters [1894CB3273; 1897LA(297)221, 1897LA(298)1; 31M106; 33M285], and iminothioesters (56JCS2253) can be used. However, as already noted, these reactions also yield, 1,2- and 1,4-dihydrotetrazines which, depending on conditions, can become the main products. Sometimes, in the synthesis of 3,5-disubstituted 4-aminotriazoles, hydrazidoylchlorides and hydrazine are used [Eq. (42)] (06JPR1, 06JPR277; 07JPR416; 84JHC797).

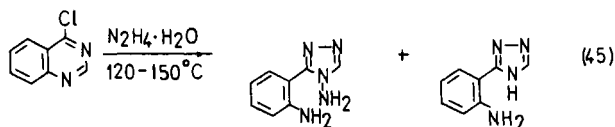
The cyclization of oxalamidrazone and oxalhydrazidine at elevated temperatures leads to the formation of 4-amino-*s*-triazole [Eq. (43)] (58JOC1931).



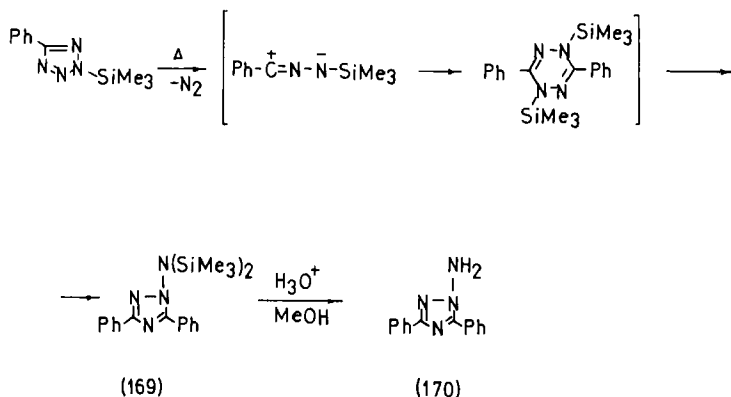
N-Amino-*s*-triazoles also can be obtained by a ring transformation of some heterocycles. For instance, hydrazine converts perfluoroalkyl 1,3,4-oxadiazoles, under mild conditions via the acyclic intermediate **168**, into 3,5-disubstituted 4-aminotriazoles [Eq. (44)] (66JOC781; 89JOC1760). A similar reaction was described also for 3-phenyl-1,3,4-oxadiazolium salts [71JCS(C)409].



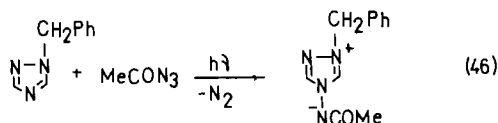
On heating 4-chloro-, 4-mercapto-, or 4-hydrazinoquinazolines with hydrazine hydrate in a sealed ampoule, the 3-(2-aminophenyl) derivatives of 4-aminotriazole and triazole are formed in yields of 66% and 22%, respectively [Eq. (45)] [72JCS(P1)1842].



Thermolysis of 2-trimethylsilyl-5-phenyltetrazole at 190°C affords triazole **169**, and the resultant acidic hydrolysis gives rise to 1-amino-3,5-diphenyltriazole (**170**); both reactions proceed in a yield of 90–95% (63CB2750).



Under similar conditions, 5-phenyltetrazole is converted to a complex mixture containing amine **164** (42%), 3,5-diphenyl triazole, and different phenyl-substituted triazines and tetrazines (62LA146). Electrophilic amination of 1,2,4-triazole by HOSA [80JCR(M)514] or by DNPH (89S269) leads to 1-amino- and 4-aminotriazole with the great dominance of the first. This is the only method to synthesize unsubstituted 1-amino-*s*-triazole. It is known as the nitrene amination of 1,2,4-triazoles [Eq. (46)] [74AHC (17)213].

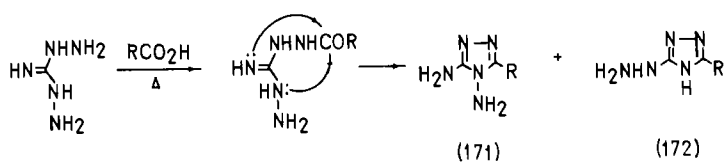


2. C-Amino and C-Hydrazino-1,2,4-triazoles

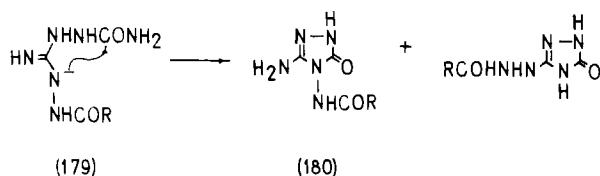
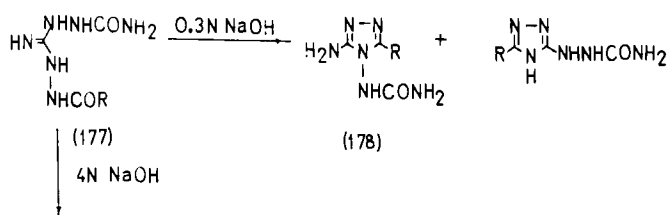
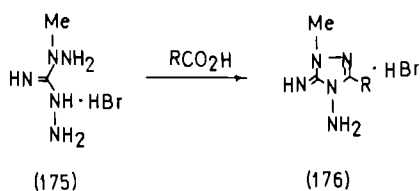
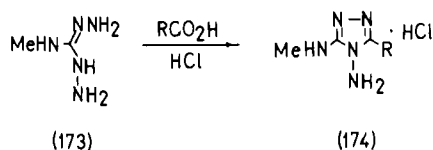
All known compounds of this type have the *N*-amino group in position 4. The main methods of synthesis are based on cyclization reactions of diamino- and triamino-guanidines. Since the latter have several unequal nucleophilic centers, reactions often give a poor yield of the corresponding *N*-aminotriazole.

At the beginning of this century, it was shown that heating diaminoguanidine with carboxylic acids leads to the formation of 3,4-diamino-5-*R-s*-triazoles (**171**) and isomeric 3-hydrazino-5-*R-s*-triazoles (**172**) (15G450). This method of synthesizing 3,4-diamino-*s*-triazoles is now widely used (79JHC1393; 85MI2; 86MI1). Obviously, the formation of 3,4-diamino-*s*-

triazoles on reduction of nitroaminoguanidine with zinc in formic or acetic acid (52MII; 53JOC218) belongs to this reaction type.

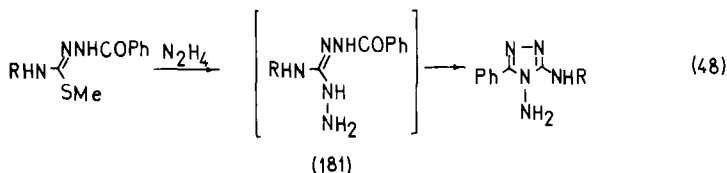
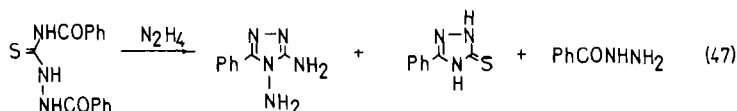


Kröger *et al.* used the isomeric *N*-methyldiaminoguanidines **173** and **175** and obtained 3,4-diaminotriazoles **174** and **176** in 37–56% and 54–85% yields, respectively (63LA156).

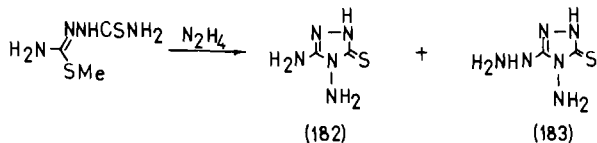


1-Carbamoyl-5-acyldiaminoguanidines (**177**) are cyclized to 4-ureido-3-aminotriazoles (**178**) in 0.3 M aqueous alkali, whereas at higher alkaline concentration, 3-amino-4-acylamino-5-ones (**180**) are formed [67LA(703)116]. Perhaps in the former case, neutral molecule **177** takes part, whereas in the latter N-anion, **179** participates. 3-Hydrazinotriazole derivatives are also formed in both reactions. The cyclization of 1-carbamoyl-(or 1-thiocarbamoyl)-5-arylidene derivatives of diaminoguanidine proceeds by a similar way (88JHC565).

Derivatives of thiosemicarbazide (50JCS614) [Eq. (47)] and *S*-methylisothiosemicarbazide (50JCS1579) [Eq. (48)] give 3,4-diamino-*s*-triazoles. Probably, the corresponding diaminoguanidine, for example **181**, is an intermediate.

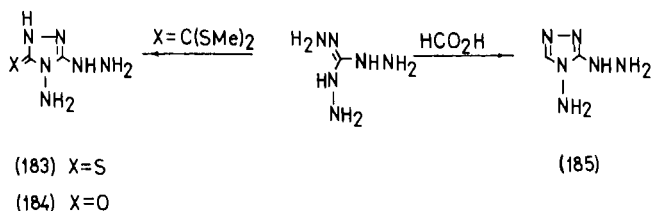


Similarly, hydrozinolysis of *S*-methylbisthiourea (65FRP1379479) and *N,N'*-dithiocarbamoyl hydrazine (52JCS4817) affords a mixture of 3,4-diamino- (**182**) and 3-hydrazino-4-amino-*s*-triazoline-5-thione (**183**). Desulfurization of diaminothione **182** by the Raney-nickel reaction yields 3,4-diaminotriazole (52JCS4817).

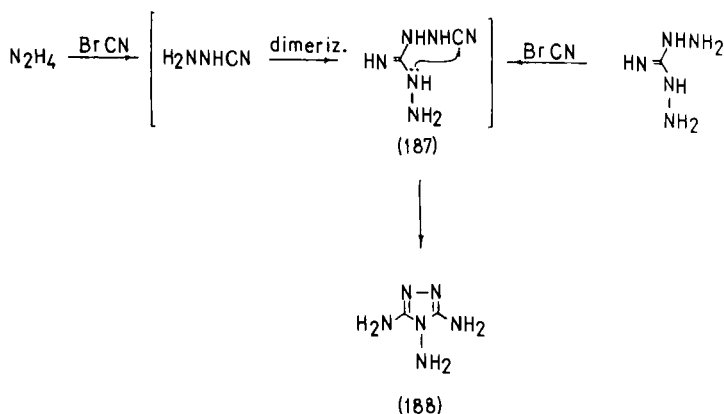
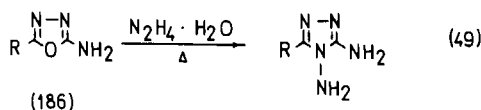


Aminohydrazine **183** can also be obtained by the reaction of thiocarbamide with hydrazine (54JOC733) or dimethyltrithiocarbonate (60ACS1037),

by recyclization of 2,5-dimercapto-1,3,4-thiadiazole under the action of hydrazine (08CB1099) and on heating triaminoguanidine with carbon disulfide (68JOC143) or dimethyltrithiocarbonate (65USP3183241). On using dimethylthiocarbonate instead of dimethyltrithiocarbonate in the latter reaction, 3-hydrazino-4-aminotriazoline-5-one (**184**) is formed. 3-Hydrazino-4-aminotriazole (**185**) unsubstituted in position 5 is obtained in 91% yield on heating triaminoguanidine with formic acid (63LA146).



Recyclization of 5-R-2-amino-1,3,4-oxadiazoles, on heating with hydrazine hydrate, leads to the corresponding 3,4-diaminotriazoles, whose yields varied from 21% to 44% [Eq. (49)] (63LA119). The reaction of oxadiazoles **186** with semicarbazide was used to synthesize 3,4-diaminotriazoline-5-one in several steps [67LA(702)101].



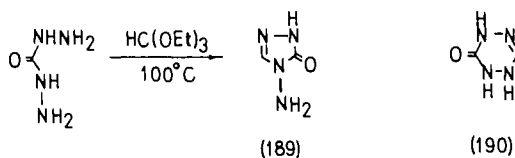
3,4,5-Triamino-*s*-triazole (aminoguanosine) (**188**) was first obtained by Pellizzari *et al.* on reaction of excess hydrazine with cyanogen bromide (05G291). However, the structure of **188** was determined two years later when the same reaction was carried out by the action of cyanogen bromide on diaminoguanidine [07G(2)317]. In both cases, the process probably proceeds via the formation of the cyano derivative of diaminoguanidine (**187**).

Other methods of synthesizing triamine **188** include the action of oxidants (PbO, HgO) on thiosemicarbazide (34JPR193; 89JHC1077), heating of *S*-methylisothiosemicarbazide with bases [54CI(L)158; 89JHC1077], or hydrazinolysis of dimethylcyanoamide (65JHC98).

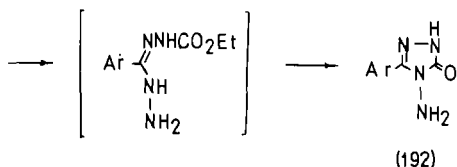
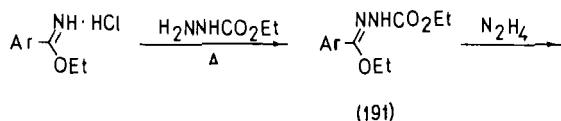
Heating of guanidine carbonate with hydrazine leads to the formation of 4-amino-3,5-dihydrazino-*s*-triazole (08CB1099).

3. 1,2,4-Triazoline-3-ones and 1,2,4-Triazoline-3,5-dione

4-Amino-*s*-triazoline-3-one (**189**) was first synthesized by Curtius and Heidenreich on heating carbohydrazide with *ortho*-formate (1894CB2684; 1895JPR454). However, in spite of chemical evidence of the presence of the primary amino group, the 1,2-dihydro-*s*-tetrazinone (**190**) structure was adopted. Later, Busch (01CB2311) and Stolle (07JPR423) found convincing proof in favor of the correct structure **189**.

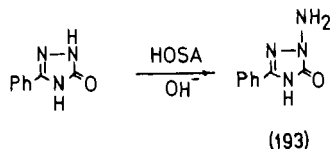
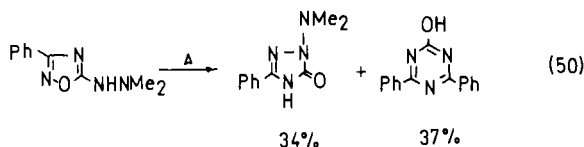


The method offered by Curtius was applied to *ortho*-esters of acetic, propionic (65CB3025), and benzoic (79JHC403) acids; this allowed him to obtain 3-methyl-, 3-ethyl-, and 3-phenyl derivatives of 4-amino-*s*-triazoline-5-one. Instead of *ortho*-esters, one can use carboxylic acids, but in this case *N,N'*-diacyl-substituted carbohydrazides are first formed, which must then be cyclized in alkali (65CB3025). Other cyclizing agents for obtaining 3-aryl-4-amino-*s*-triazoline-5-ones include trihalogenmethanes ArCCL₃ (79JHC403) and iminoesters (79JHC403; 83MI1; 84JHC1769). On using iminoesters, carbohydrazide can be superseded with ethyl hydrazinecarboxylic ester. The intermediate hydrazone **191** undergoes hydrazinolysis, affording 4-amino-3-aryltriazoline-5-ones (**192**) in a yield of 60–95% (79JHC403; 83MI2; 84JHC1769).



Other syntheses of 3-aryl-4-amino-*s*-triazoline-5-ones make use of hydrazinolysis of 1-thiobenzoylcarbohydrazide [75JCS(P1)1781], oxidation of 1,5-dibenzylidenecarbohydrazide (80JHC1691), and recyclization of 2,4-disubstituted 1,3,4-oxadiazoline-5-ones under the action of hydrazine (68ZC221).

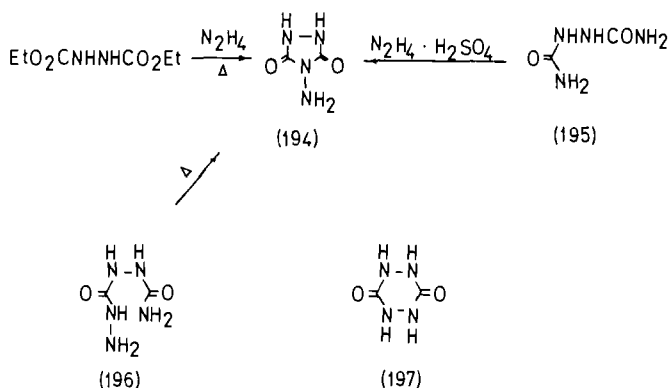
The formation of 1-amino-*s*-triazoline-5-ones in low yield on thermolysis of 3-phenyl-5-hydrazino-1,2,4-oxadiazoles [Eq. (50)] [81JCS(P1)1703] is known. The best method of synthesizing 1-aminotriazolinones includes direct amination of 3-*R*-triazolinones. Thus, amine **193** was obtained in 76% yield [81JCS(P1)1703].



Many 1-alkyl-3-*R*-4-amino-*s*-triazoline-5-ones were obtained by alkylation of the N-anions of 4-amino-3-*R*-*s*-triazoline-5-ones (80JHC1691; 83MI2; 84JHC1769).

The history of the synthesis of 4-amino-*s*-triazoline-3,5-dione (4-aminourazole) (**194**) is intricate. Curtius and co-workers were the first to

synthesize it by hydrazinolysis of diethyl hydrazinedicarboxylate (1894CB2684). Later, the same compound was obtained by Purgotti, on heating bisurea **195** with hydrazine sulfate (1897G60), and by Pellizzari and Roncagliolo on heating ureidosemicarbazide **196** [07G(I)434]. All the authors described this compound not as amine **194**, but as tetrazinedione **197** known under the name urazine. Busch and Grohmann (01CB2320) and Stolle (07JPR416) argued in favor of the correct structure **194**. However, almost all investigators were convinced of the correctness of structure **197** for many decades. Thus, even in 1953, Andrieth and Mohr obtained amine **194** in a yield of 73%, on heating carbohydrazide in hydrochloric acid, and described this compound as **197** (53MI2).



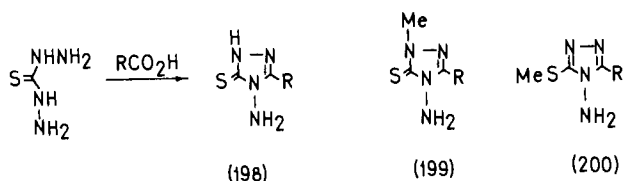
In 1959, Belgian chemists worked out another method of synthesizing amine **194** by heating phenyl hydrazinecarboxylate (59BSB432). These authors, and then Lutz (64JOC1174), finally proved that the product obtained in all cases described earlier has structure **194**. The results of Guha and De (24JCS1215) were revised, since they proposed the formation of urazine **197** from carbohydrazide with urea. The product thus obtained was found to be bisurea **195**.

The synthesis of urazine **197** as the result of heating hydrazine and carbon dioxide under high pressure in an autoclave have been reported (49JCS1156). On the basis of the facts described here, it seems more probable that this product is also *N*-aminotriazole **194**.

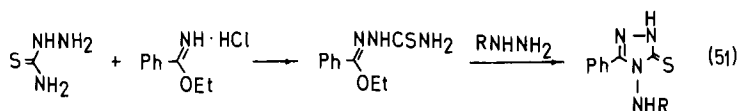
4. 1,2,4-Triazoline-3-thiones and 1,2,4-Triazoline-3,5-dithione

Stolle and Bowles were the first to synthesize 4-amino-*s*-triazoline-3-thione (**198**, R = H) on heating thiocarbohydrazide with *ortho*-formate (08CB1099). Their data were supported by Beyer and Kröger, who used

ortho-esters of the other carboxylic acids as well as their amides and esters (60LA135). The latter authors showed that the best yield (75–80%) of aminothiones **198** can be reached on refluxing thiocarbohydrazine with the carboxylic acids. It is possible to use iminoesters in this reaction (59GEP1058844). In the case of acetic anhydride, a mixture of 1-acetyl-4-acetamino- and 1-acetyl-4-diacetimido-aminothiones (**198**) is formed. 2-Methylthiocarbohydrazide and *S*-methylisothiocarbohydrazide react with carboxylic acids, yielding the isomers **199** and **200**, respectively (61LA121).

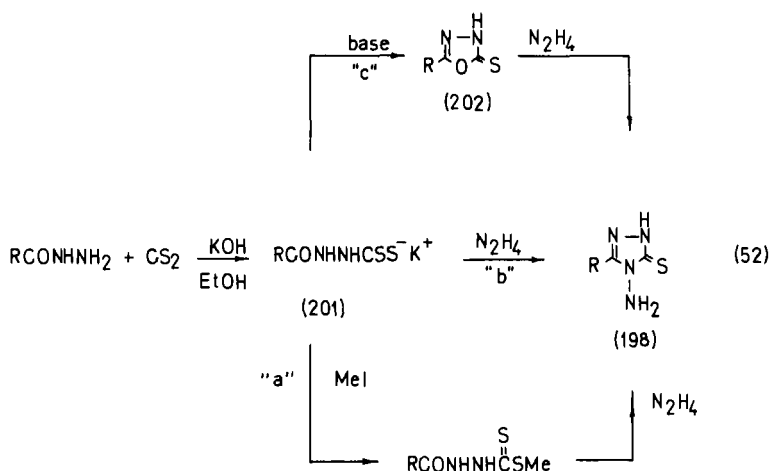


Other methods of synthesizing 4-amino-*s*-triazoline-3-thiones are as follows: the reaction of thiocarbohydrazide with sodium salts of dithiocarboxylic acids (54CB825), the cyclization of 1-thiobenzoylthiocarbohydrazides under alkaline conditions [75JCS(P1)1787], the recyclization of 1,3,4-thiadiazoles by hydrazine [62YZ683; 68JCS(C)2099], the two-step cyclization of thiosemicarbazide by iminoesters or *ortho*-esters [Eq. (51)] (55YZ1149; 56JA1973; 84JHC1689).



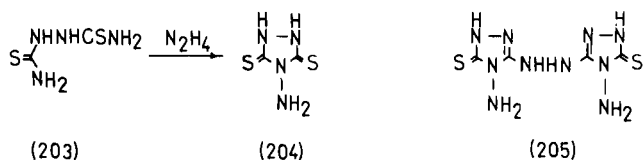
Presently, the synthesis of 5-*R*-4-amino-*s*-triazoline-3-thiones is often carried out by the Hoggarth method (52JCS4811), where hydrazides are treated with carbon disulfide in potassium hydroxide-alcohol solution affording potassium acylthiocarbazates (**201**). The latter compounds are methylated, and then the methyl esters are cyclized on heating with hydrazine [pathway a, Eq. (52)]. Reid and Heindel simplified this method by cyclizing salts **201** with hydrazine [pathway b, Eq. (52)] (76JHC925). They proposed another modification of the Hoggarth method involving the preliminary transformation of acyldithiocarbazates **201** to thio derivatives of 1,3,4-oxadiazole (**202**), followed by recyclization by hydrazine [pathway c, Eq. (52)]. The authors also suggested the formation of oxadiazoles **202** as intermediates on treatment of salts **201** with hydrazine. Although there

is no proof of this proposal, patients describe conversions of oxadiazoles **202** to **198** by hydrazine (56GEP953802).



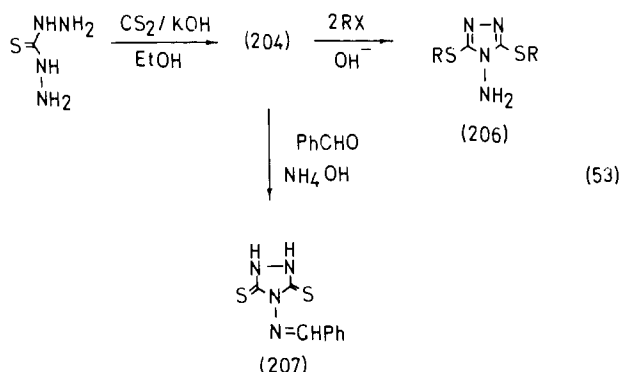
The Hoggarth method and its modifications, mainly pathway b, were used to synthesize a large series of 5-alkyl-, 5-hetaryl-, and especially 5-aryl derivatives of 4-amino-*s*-triazoline-3-thione [56YZ1133; 66JOC3528; 69JCS(C)1218; 71JMC335; 72JHC1169; 73JHC103; 80JOC2479; 84JHC1225; 86JHC1451; 89JHC177].

The synthesis of 4-amino-1,2,4-triazoline-3,5-dithione (**204**) was first carried out by Purgotti and Vigano on hydrazinolysis of dithiourea **203**. However, the product thus obtained was mistakenly described as 1,2-dihydro-*s*-tetrazinedithione (01G563). Stolle repeated the Purgotti experiments and determined the correct structure to be **204** (07JPR423). These results were also rechecked by Arndt and Beilich, who obtained dithione **204** only on using a large excess of hydrazine (23CB809); as side products, they isolated monothione **182** and hydrazo compound **205**.

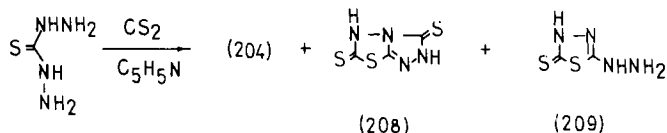


The best method of synthesizing aminodithione **204** is from thiocarbonyldrazide with potassium ethylxanthate [Eq. (53)]. Guha and De first carried

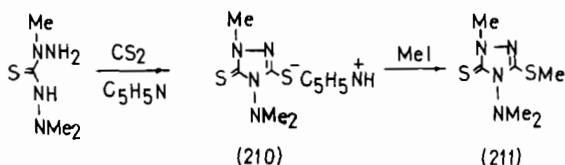
out this reaction on heating the mixture of thiocarbohydrazide and carbon disulfide with alcoholic potassium hydroxide in a sealed ampoule (24JCS1215). The product thus obtained was readily alkylated on both sulfur atoms affording **206**, but did not give the Schiff base with benzaldehyde. The latter caused assignment of the 1,2-dihydro-*s*-tetrazinedithione structure to this compound. Only at the beginning of the 1960s did three groups of chemists independently determine that Guha had synthesized 4-amino-*s*-triazoline-3,5-dithione (**204**) (61ACS1295, 61ZN767; 64JOC1174). Guha did not obtain the Schiff base because of poor solubility of compound **204**. Carrying out the reaction of benzaldehyde with the ammonium salt of dithione (**204**), Lutz obtained azomethine **207** (64JOC1174).



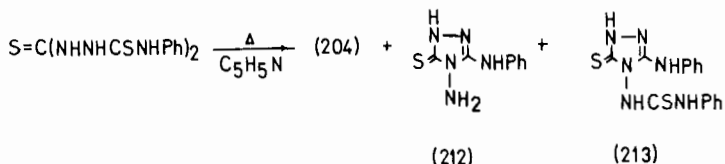
Sandström used pyridine instead of alcoholic potassium hydroxide to synthesize **204** by the Guha method (61ACS1295). Thus, refluxing thiocarbohydrazide with carbon disulfide in pyridine led to the formation of aminodithione **204** (50%) along with the bicyclic compound **208** (40%) and a small amount of 1,3,4-thiadiazole **209**.



Similarly, a trimethylthiocarbohydrazide gave the salt **210** in almost quantitative yield, and the methylation of this salt led to 1-methyl-3-methylthio-4-dimethylamino-*s*-triazoline-5-thione (**211**) (68ACS309).

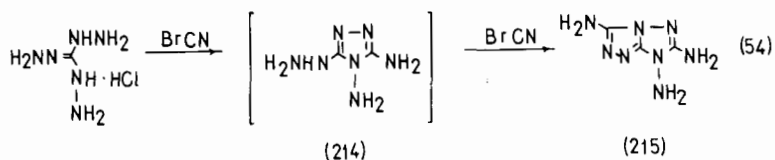


Refluxing 1,5-di(phenylthiocarbamoyl)thiocarbohydrazide in pyridine gives rise to **204**, **212**, and **213** in yields of 44%, 33%, and 7%, respectively (66CB81).



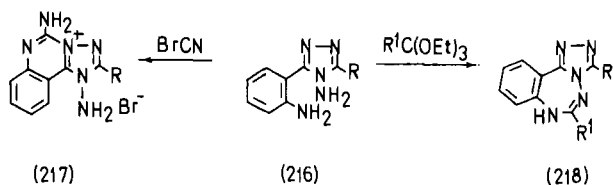
5. Condensed 1,2,4-Triazoles

One of the first representatives of this series was 3,6,7-triamino-7*H*-1,2,4-triazolo[5,1-*c*]-1,2,4-triazole (**215**), obtained in high yield on interaction of traininoguanidinium hydrochloride with excess cyanogenbromide [Eq. (54)] (68JOC143). Diaminohydrazine **214** was proposed as the intermediate in this reaction. This is supported by the cyclization of authentic aminohydrazine (**214** to **215**) or related compounds by the action of cyanogenbromide, formic acid, or carbon disulfide in alkaline medium.

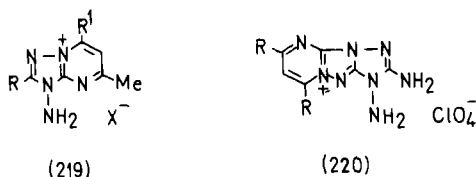


An interesting feature of this reaction is that the *N*-amino group does not take part in the cyclization. This is also observed in other cases. Thus, cyanogenbromide and 4-amino-3-(*o*-aminophenyl)-*s*-triazoles (**216**) give the condensed *N*-aminotriazoles (**217**), whereas the reaction of **216** with *ortho*-esters proceeds with participation of both amino groups and results in triazepine **218** (73TL1643).

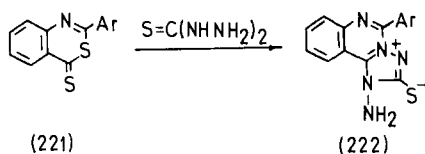
On short heating with excess acetyl- or benzoyl-acetone, hydrochlorides of 3,4-diamino-1,2,4-triazoles are converted to 1-aminotriazolo[2,3-*a*]pyri-



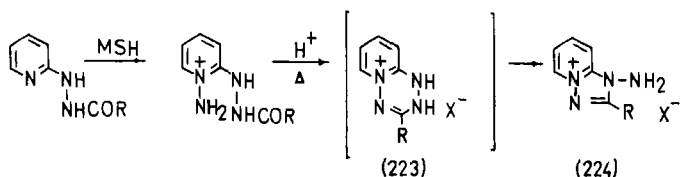
midinium salts (**219**) (73UKZ1036, 73UKZ1040). Similarly, compound **215** gives **220** (80UKZ1092).



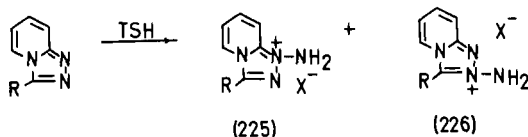
Recyclization of benzo-1,3,-thiazine-4-thiones (**221**) by the action of thiocarbonylhydrazide yields mesoionic condensed triazole *N*-amino derivatives (**222**) (86JHC43).



By the action of MSH, 2-(2-acylhydrazino)pyridines are transformed to *N*-aminopyridinium salts. These cyclized to 1-aminotriazolo[1,5-*a*]pyridinium salts (**224**) in acid. The latter compounds can also be obtained by the direct amination of the corresponding 2-*R*-triazolo[1,5-*a*]pyridines with MSH or TSH [76JCS(P1)367]. The cyclic contraction in 1,2-dihydro-*s*-tetrazines discussed earlier suggest the intermediate formation of dihydrazine **223**.

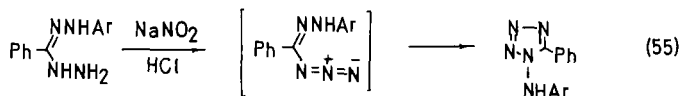
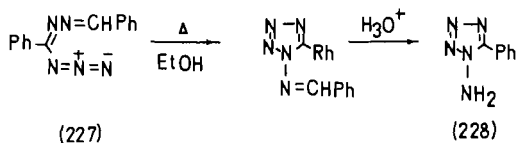


3-R-1,2,4-Triazolo[4,3-*a*]pyridines are aminated by TSH, affording only 1-aminotriazolium salts **225** (R = H, Ph) or a mixture of salts **225** and **226** (R = Me) in a ratio of 9 : 1 [76JCS(P1)367].



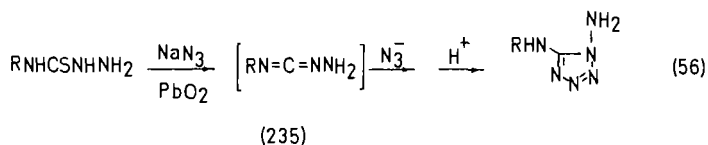
G. N-AMINOTETRAZOLES

Methods based on cyclization, recyclization, or direct amination were developed to synthesize *N*-aminotetrazoles. Almost all these reactions lead to 1-aminotetrazoles, and only the *N*-amination of tetrazoles also involves the formation of 2-amino derivatives. For the cyclizations, geminal azidohydrazones of type $\text{N}_3\text{—C=N—NHR}$ or $\text{N}_3\text{—C=N—N=CRR'}$ are used as a basis. Thus, on heating in alcohol, benzalbenzhydrazide **227** is converted to 1-benzylideneamino-5-phenyltetrazole, hydrolysis of which yields amine **228** (14CB1132). Other 1-amino-5-aryltetrazoles (22CB1297; 33JPR1) as well as 1-arylaminotetrazoles can be obtained similarly [Eq. (55)] (62T1001). The products of Eq. (55) were first mistakenly described as 2,6-diaryl-2,5-dihydropentazines (26JCS113).

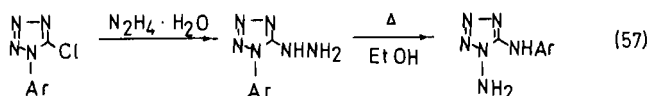


The symmetrical dibenzhydrazide dichloride (**229**) was used in a two-step synthesis of 5,5'-diphenyl-1,1'-ditetrazolyl (**230**) and 1-benzoylamino-5-phenyltetrazole (**231**) (62CB2546). The yield at both stages was almost

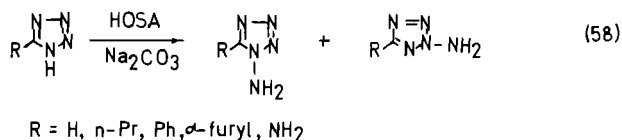
stead of thiosemicarbazide as the initial compound yields 1-amino-5-hydrazinotetrazole (31JPR209).



1-Aryl-5-hydrazinotetrazoles, obtained by the action of hydrazine hydrate on 1-aryl-5-chlorotetrazoles, undergo the Dimroth rearrangement on heating in alcohol, resulting in 1-amino-5-arylaminotetrazoles [Eq. (57)] (88BSB543).



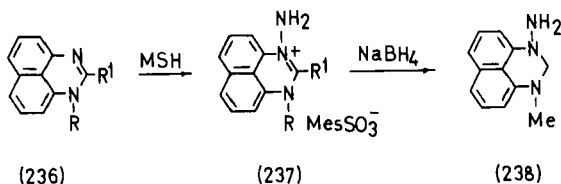
Tetrazole and its 5-substituted derivatives are aminated by HOSA in aqueous sodium carbonate to afford a mixture of 1- and 2-aminotetrazoles in yields of 40–50% [Eq. (58)] (69CJC3677). The amination of 5-aminotetrazole is less successful, and the total yield of 1,5- and 2,5-diaminotetrazoles is not greater than 13%. Usually, the yield of 1-aminotetrazole is 1.5–2 times greater than that of the 2-isomer. An exception is 5-phenyltetrazole, which presents the opposite result.



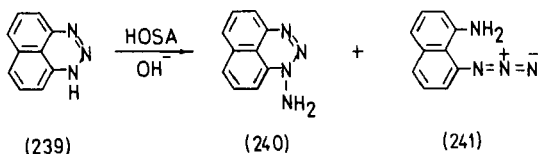
H. N-AMINO DERIVATIVES OF PERI-CONDENSED NH-HETEROCYCLES

The structural similarity to azoles and the resemblance of many physico-chemical properties allow one to consider peri-codensed NH-heterocycles of the perimidine type (236) as analogues of azolo heterocycles (85KGS867). Under the action of MSH, perimidine and its substituted derivatives give the quaternary salt **237** in good yield (80KGS93; 83CPB1378). One of these salts was converted to 1-methyl-3-amino-2,3-

dihydroperimidine (**238**) by sodium borohydride (80KGS93). An attempt to synthesize the base of 1-aminoperimidine using HOSA in alkaline medium failed (80KGS93).



Unlike perimidine, naphtho[1,8-*d,e*]triazine (**239**) is readily aminated by HOSA, affording 1-amino derivative **240** and 1-amino-8-azidonaphthalene **241** in yields of 37–46% and 12–26%, respectively [69JCS(C)756, 69JCS(C)769]. Azide **241** is formed on decomposition of the unstable 2-aminonaphtho-[1,8-*d,e*]triazine in alkaline medium. The latter compound can be isolated in low yield on cautious amination of the sodium salt of amine **239** [69JCS(C)756]. By cyclization of 1-amino-8-hydrazinonaphthalene hydrazones, the hydrazones of amine **240** were obtained; however, it was impossible to convert the latter hydrazones to the free amine, probably because of the low stability of such an amine under acidic conditions [68JAI923; 69JCS(C)769].

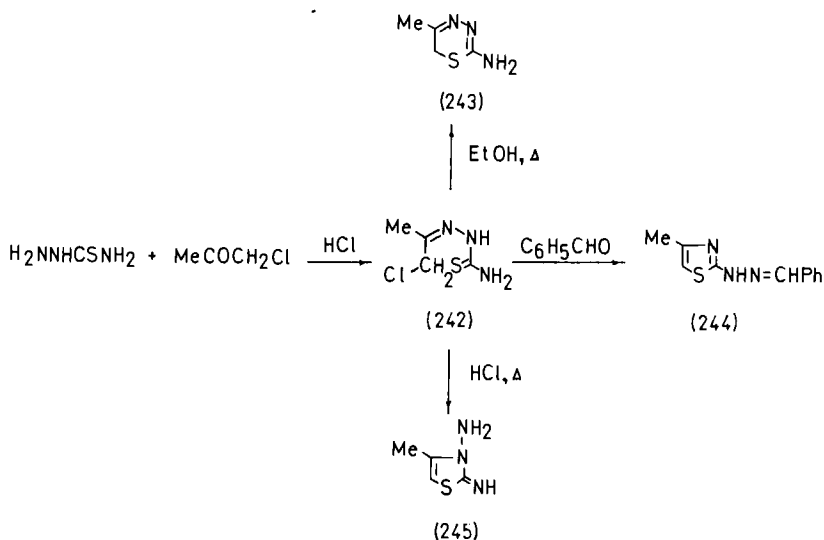


I. N-AMINO DERIVATIVES OF THIAZOLES, THIADIAZOLES, AND OXAZOLES

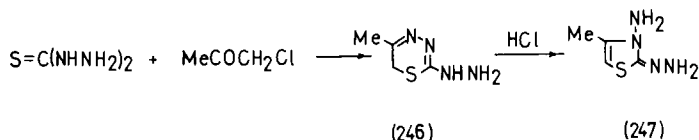
The first syntheses of *N*-aminothiazoles were based on cyclization. As starting compounds, one could use thiosemicarbazide, thiocarbohydrazide, dithiocarbohydrazide and their derivatives interacting with α -halogenocarbonyl compounds. Thus, McLean and Wilson carried out the reaction of thiosemicarbazide with chloroacetone and described the compound thus obtained as 1,3,4-thiadiazine **243** (37JCS556). However, Beyer and co-workers showed that the course of this reaction is hard to define

and, depending on conditions, can lead to different products including *N*-aminothiazole derivatives (54CB1385).

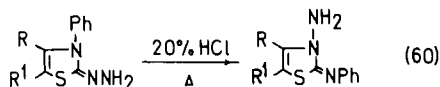
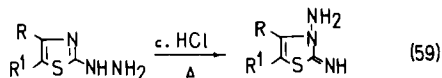
If the reaction of thiosemicarbazide with chloroacetone is carried out in a warm dilute solution of hydrochloric acid, the thiosemicarbazone of chloroacetone (**242**) is formed in 85% yield. Heating **242** in ethanol cyclizes it to thiadiazine **243**, whereas heating in anhydrous ethanolic benzaldehyde yields the benzylidene derivative of 4-methyl-2-hydrazinothiazole (**244**). At the same time, refluxing **242** in concentrated hydrochloric acid gives rise to 4-methyl-3-aminothiazoline-2-imine (**245**) in 95% yield. The latter compound can be also obtained by the action of concentrated HCl on thiadiazine **243**. On using various α -halogenoketones and thiosemicarba-



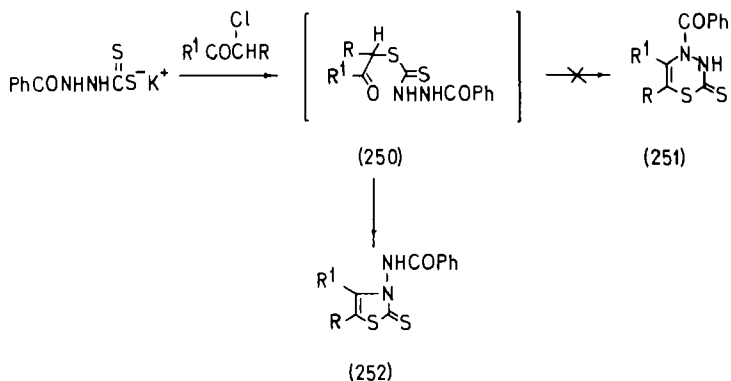
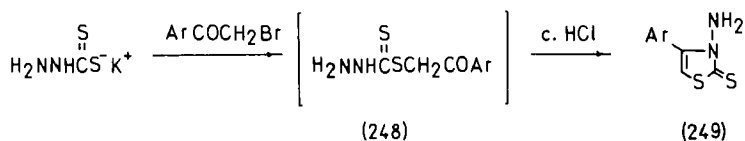
zide, one can also synthesize other 4(5)-substituted 3-aminothiazoline-2-imines by this method (53G296; 54CB1392; 56CB1652; 73JPR79). Changing thiosemicarbazide to thiocarbohydrazide leads to 3-amino-4-methylthiazolone-2-hydrazone (**247**) via thiadiazine **246** (54CB1401).



2-Hydrazinothiazoles (54CB1392) and 2-arylthiazolone-2-hydrazones (59JPR265) are recycled into the corresponding 3-aminothiazoline-2-imines on heating with hydrochloric acid [Eqs. (59) and (60)].



3-Aminothiazoline-2-thiones are synthesized from potassium dithiocarbazate (54AK249; 87H1323) or potassium benzoyldithiocarbazate (57YZ771; 67AG618) obtained *in situ* by the action of carbon disulfide on hydrazine or benzoylhydrazine. The alkylation of potassium salts by α -halogenocarbonyl compounds leads to intermediates **248** or **250**, which are cyclized to the corresponding 3-aminothiazoline-2-thiones (**249**) and (**252**) in acidic medium. The product **252** was first mistakenly described as a thiadiazine (**251**) (57YZ771), but the structure was corrected in favor of the *N*-aminothiazole (66AG841; 67AG618).



N-Aminothiazolium salts **253** are obtained by the amination of thiazoles with the use of MSH (73JHC947; 74CPB482, 74JHC459, 74S126). Similarly, one can synthesize the salts of 3-amino-2-*R*-benzothiazolium (*R* = H, Me, Ph, NHAc) (73JHC947; 74S126), 2,3-diaminonaphtho[1,2-

known. Information about dipole moments and ^{15}N -NMR spectral data on unsubstituted *N*-aminoazoles are practically absent. However, available data, especially based on UV and IR spectroscopy, allows one to draw some substantial conclusions on the nature of electron interaction between the *N*-amino group and the azole nucleus. It also allows one to understand the main peculiarities of the chemical behavior of *N*-aminoazoles.

A. AGGREGATE STATE, MELTING POINT TRENDS, AND SOLUBILITY

Most *N*-aminoazoles are crystalline compounds. Only 1- and 2-aminotetrazoles, 1-aminopyrazole, and some of its simple *C*-alkyl derivatives are liquids under usual conditions. Most *N*-aminoazoles are stable; many of them can be distilled in a vacuum without decomposition. However, *N*-aminotetrazoles can explode (69CJC3677).

Judging by X-ray structural analysis (71ZC179) and melting points, *N*-aminoazoles associate by intramolecular hydrogen bonds. Thus, 1-aminobenzimidazole is a crystalline compound with m.p. 156–157°C, whereas 1-dimethylaminobenzimidazole is an oil. For the same reason, *N*-aminoazoles melt, as a rule, at higher temperatures than the corresponding *N*-alkylazoles (Table V). The *N*-aminoazole aggregates are not as strong as the aggregates of parent azoles, since the melting points of the latter compounds are usually a little higher. The only exceptions are 1,2,3-triazoles and their *N*-amino derivatives (Table V).

As regards solubility, *N*-aminoazoles occupy also an intermediate position between azoles and *N*-alkylazoles. For instance, *N*-aminoazoles as well as azoles have good or moderate solubility in polar solvents (water, alcohol). But at the same time, many *N*-aminoazoles as well as *N*-alkylazoles show good solubility in benzene and heptane and often can be recrystallized from them.

B. CRYSTAL STRUCTURE AND QUANTUM CHEMICAL CALCULATIONS

X-Ray structural investigations on some *N*-aminoazoles, namely *N*-aminopyrazoles [89AX(C)1902], 1-amino-1,2,3-triazoles (71ZC179), 4-amino-1,2,4-triazoles (89JOC1760), 9-amino-1-methylxanthine (87KGS-836), and 1-aminobenzimidazole and 2-aminobenzotriazoles [90JCS(P2)-237] have been reported. In the last two papers it was shown that *N*-aminogroup has a pyramidal configuration, as in hydrazine. The axis of

TABLE V
MELTING POINTS (°C) OF SOME AZOLES
AND THEIR *N*-METHYL- AND *N*-AMINO DERIVATIVES

Azole	Unsubstituted ^{a,b}	<i>N</i> -Methyl ^{a,b}		<i>N</i> -Amino	
		1-Me	2-Me	1-NH ₂	2-NH ₂
Pyrazole	70	b.p. 127		b.p. 71 (15mm) ^c	
Indazole	146–147	60–61	56	108–109 ^d	97–99 ^d
Benzimidazole	170	61	–	156–157 ^e	–
1,2,3-Triazole	23	15–16	22	51 ^f	–
Betzotriazole	98–99	64–65	b.p. 104 (15mm)	84 ^g	121–122 ^g
1,2,4-Triazole	120–121	20	90(4-Me)	86–88 ^h	81–82 (4-NH ₂) ^a
Tetrazole	158	38–39	9–10	b.p. 137–142 (0.7mm) ⁱ	b.p. 89–91 (0.3mm) ⁱ

^a (76MI1)^b (82MI1)^c (85LA1732)^d [75JCS(P1)31]^e (89KGS221)^f (09CB659)^g [69JCS(C)742]^h [80JCR(M)514]ⁱ (69CJC3677)

the vacant electron pair is located in the plane of the azole system, and the hydrogen atoms are arranged on different sides of this plane. Evidently with such geometry, conjugation between the *N*-amino group and the π -system of the ring should be at a minimum. These data are in good agreement with quantum chemical energy calculations for various *N*-aminoazole conformers made with the use of both nonempirical and modified neglect of differential overlap (MNDO) methods (89KGS1221).

There are X-ray structural data on *N*-benzoyl- [72JCS(P2)662], *N,N*-dibenzoyl- [75AX(B)2788], and *N*-tosyl derivatives (89JHC301) of 1-amino-1,2,3-triazole and on the 1-(*N*-aziridiny)benzimidazole derivative (86CC832). In these compounds, the nitrogen atom of the amino group is also pyramidal.

Semiempirical quantum chemical calculations using the complete neglect of differential overlap (CNDO/2) method were made for 1,2-diaminoimidazole (84KGS1396), 1,2-diaminobenzimidazole (85KGS1402), 1-acylamino-1,2,3-triazoles (87JHC1461), and *N,N'*-diazolyls [80JCR(M)-514].

C. BASIC STRENGTH AND SITE OF PROTONATION

Theoretically, *N*-aminoazoles can be protonated on either the *N*-amino group or on the azole nucleus. The preferred place of protonation can be obtained by analysis of their pK_a constants. pK_a values for a series of *N*-aminoazolium ions in acetonitrile are presented in Table VI. Extrapolation of these pK_a values to aqueous solution shows they must decrease by about 7.5. Since 1-methylindole is not protonated in acetonitrile, it is evident that the pK_a value of 6.55 for this compound pertains to the protonated amino group.

This value is several orders of magnitude less than that for protonated hydrazine. This is evidence for a very strong electron-withdrawing influence of the *N*-indolyl substituent on the amino group. One can assume that such an influence is mainly due to inductive character. Taking into account that the electron-withdrawing effect of the *N*-azolyl substituent is greater than that of the *N*-indolyl group [87AHC(42)1], there is no doubt that the base strength of the *N*-amino group must be even less in *N*-aminoazoles than in 1-aminoindole. Therefore, the relatively high pK_a values for the *N*-amino derivatives of benzimidazole, indazole, and theophylline provide evidence that protonation takes place on the ring nitrogen atom.

The basicity of all the *N*-aminoazoles is a little less than the base strength of the corresponding *N*-methylazoles (Table VI). This shows the slight

TABLE VI
 pK_a VALUES (IN MeCN, 20°C) OF SOME
N-AMINO- AND *N*-METHYL- AZOLIUM IONS^a

Heterocycle	Substituent	pK_a
Indole	1-NH ₂	6.55
Benzimidazole	1-Me	13.50
Benzimidazole	1-NH ₂	12.83
Benzimidazole	1-NMe ₂	12.40
Indazole	1-Me	6.85
Indazole	1-NH ₂	6.70
Indazole	2-Me	9.26
Indazole	2-NH ₂	8.64
Theophylline	7-Me	7.60
Theophylline	7-NH ₂	7.20
Theophylline	9-Me	9.91
Theophylline	9-NH ₂	9.30

^a (89KGS221)

electron-withdrawing effect of the *N*-amino group relative to methyl. A stronger electron-acceptor effect is exhibited by the *N*-azolyl groups in *N,N'*-diazolyls. Thus, the pK_a value for 1-(*s*-triazolyl-4)-benzimidazole, protonated on the imidazole ring, is equal to 1.34 (in aqueous solution). That is considerably lower than the value for benzimidazole (pK_a 5.55) [85JCS(P1)1209].

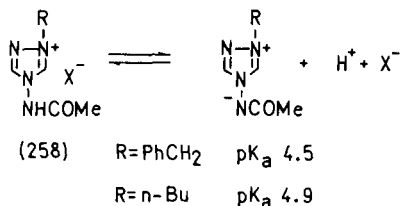
A number of pK_a values have been measured for some 4-amino-1,2,4-triazoles in 50% aqueous methanol (80JHC1691). The pK_a value for the unsubstituted amine (pK_a 2.27) is a little different from that of 1,2,4-triazole (pK_a 2.30 in water). This obviously points to protonation on the ring nitrogen atom.

Latvian chemists calculated by the Slater-type orbitals, three Gaussian (STO-3G) basis set the proton affinities for 1-aminopyrrole and *N*-aminoazoles (89KGS1221).

D. NH-ACIDITY

An indicator method was used to measure the equilibrium NH-acidity values of 1-aminobenzimidazole (pK_a 28.4), 1-aminoindazole (pK_a 28.6), 2-aminoindazole ($pK_a \sim 24$), and 7-aminotheophylline (pK_a 23.3) (89KGS221). The measurements made using dimethoxyethane can be converted to an absolute scale of acidity in dimethyl sulfoxide (DMSO) by increasing the pK_a value by 1.5. The NH-acidity values for *N*-aminoazoles are considerably greater than for ammonia ($pK_a \sim 41$ in DMSO), but are similar to the value for aniline (pK_a 30.7). It is known that the acidifying action of the phenyl group is summed up almost equally by its inductive and mesomeric effects. Therefore, the acidity value for ammonia is increased by phenyl or by benzazolyl groups almost by the same amount. Perhaps this represents the inductive effect of the benzazolyl groups.

A high NH-acidity is observed for 4-acetylamino-1-*R*-1,2,4-triazolium salts (**258**) (72ZC250). Values are similar to the acidity of acetic acid, which is some 10 orders of magnitude greater than that for acetamide.



E. ELECTROCHEMICAL PROPERTIES

Using the cyclic voltamperometric method, oxidation potentials of some *N*-aminoazoles have been measured (Table VII). All compounds thus investigated give only a one-electron oxidation wave. The oxidation process is practically irreversible, and this represents instability in the radical-cations thus formed. Comparison of the oxidation of *N*-amino- and *N*-methyl-benzazoles indicates that the *N*-amino groups decreases the E_{pa} value on the average by 0.2 V. Probably, this is explained by an overlap of the heterocycle π -orbitals with that of the unshared electron pair of the amine nitrogen atom, providing some stabilization of the radical-cation.

1-Aminoindole is oxidized the most easily. The oxidation potentials of the *N*-amino derivatives of benzimidazole, indazole, and theophylline are a little greater, all being similar. Obviously, the data show the detachment of an electron from a π -orbital of the heterocyclic system and not from the *n*-orbital of the amino group.

F. DIPOLE MOMENTS

So far, there are no data on dipole moments of unsubstituted *N*-aminoazoles. Measurement of dipole moments of *N,N'*-diazoles [80JCR(M)514],

TABLE VII
 E_{pa} ^a OF *N*-AMINO AND *N*-METHYL DERIVATIVES OF
SOME CONDENSED AZOLES^b

Heterocycle	Substituent	E_{pa} (V)
Indole	1-Me	1.18
Indole	1-NH ₂	0.95
Benzimidazole	1-Me	1.68
Benzimidazole	1-NH ₂	1.44
Indazole	1-Me	1.62
Indazole	1-NH ₂	1.12
Indazole	2-Me	1.42
Indazole	2-NH ₂	1.42
Theophylline	7-Me	1.62
Theophylline	7-NH ₂	1.40
Theophylline	9-Me	1.46
Theophylline	9-NH ₂	1.47

^a E_{pa} , potentials of anodic oxidation.

^b MeCN, 20°C vs. SCE (89KGS221).

1-(α -aroyloxyarylideneamino)-1,2,3-triazoles [77JCS(P2)1779; 79JHC571], and 1-(*N,N*-diaroylamino)-1,2,3-triazoles (83JHC1469) was reported with the goal of investigating conformations. The Spanish chemists have conducted theoretical calculations of dipole moments of 17 different *N*-aminoazoles [90JCS(P2)237].

G. SPECTRA

1. Infrared Spectra

Practically all reported IR spectra were recorded for solid samples. Therefore, the position of *N*-amino group bands is affected to some extent by the intermolecular hydrogen bonds. However, the information unambiguously shows the sp^3 -hybridization (or close to this) of the nitrogen atom in the amino group of *N*-aminoazoles. The symmetric and antisymmetric stretching bands of the NH_2 group appear in the regions 3200–3350 and 3120–323 cm^{-1} , respectively (Table VIII). This is considerably lower than for *C*-aminoazoles and approximately corresponds to the frequencies for ammonia, hydrazine, and alkylamines. As a rule, the ν_{as} peak is more intense and sharp than the ν_s peak. IR spectra of some *N*-aminoazoles, measured in carbon tetrachloride solution, reveal almost the same tendencies (88SA283).

TABLE VIII
N—H STRETCHING VIBRATION IN SOME *N*-AMINOAZOLES (IN NUJOL)

Heterocycle	Substituent	νNH_2	Footnotes
Indazole	1- NH_2	3300, 3200	<i>a</i>
Indazole	2- NH_2	3240, 3160	<i>a</i>
Benzimidazole	1- NH_2	3305, 3120	<i>b</i>
Benzotriazole	1- NH_2	3230, 3130	<i>c</i>
Benzotriazole	2- NH_2	3285, 3140	<i>c</i>
Purine	9- NH_2	3200, 3130	<i>d</i>
Theophylline	7- NH_2	3340, 3230	<i>e</i>
Theophylline	9- NH_2	3325, 3225	<i>e</i>

^a [75JCS(P1)31]

^b (89KGS221)

^c [69JCS(C)742]

^d (60JA4592)

^e (89TH1)

2. Ultraviolet Spectra

Electronic absorption spectra of *N*-aminoazoles and related *N*-alkylazoles are practically identical. This fact is one more piece of evidence testifying to the absence of marked conjugation between the *N*-amino group and the azole nucleus. This was demonstrated, for instance, for the *N*-amino derivatives of purine (69JOC1025), xanthine (89KGS221; 90ZOR1322), benzimidazole and indazole (89KGS221), benzotriazole [69JCS(C)742], and 1,2,3-triazole (71JPR882). For azoles which can be aminated on different nitrogen atoms, electronic spectra are good for structure determination of the corresponding *N*-amino derivatives (69JOC1025; 90ZOR1322).

3. Nuclear Magnetic Resonance Spectra

The proton signals of the NH₂ group are the most interesting in the ¹H-NMR spectra of *N*-aminoazoles (Table IX). Usually, these signals appear as a slightly broadened singlet at 4.80–8.30 ppm, depending on the electron-acceptor effect of the *N*-azolyl substituent. Boundaries of this

TABLE IX
PROTON CHEMICAL SHIFTS FOR *N*-AMINO GROUP IN *N*-AMINOAZOLES

Heterocycle	Substituent	Solvent	⁵ NH ₂ (ppm)	Footnotes
Pyrazole	1-NH ₂	CDCl ₃	5.55	<i>a</i>
Indazole	1-NH ₂	CDCl ₃	5.41	<i>b</i>
Indazole	2-NH ₂	CDCl ₃	6.00	<i>b</i>
Benzimidazole	1-NH ₂	CDCl ₃	4.84	<i>c</i>
1,2,4-Triazole	1-NH ₂	DMSO-d ₆	6.60	<i>d</i>
1,2,4-Triazole	4-NH ₂	DMSO-d ₆	6.23	<i>d</i>
Benzotriazole	1-NH ₂	DMSO-d ₆	5.94	<i>e</i>
Benzotriazole	2-NH ₂	DMSO-d ₆	8.28	<i>e</i>
Tetrazole	1-NH ₂	DMSO-d ₆	7.10	<i>f</i>
Tetrazole	2-NH ₂	DMSO-d ₆	7.97	<i>f</i>
Theophylline	7-NH ₂	DMSO-d ₆	6.30	<i>g</i>
Theophylline	9-NH ₂	DMSO-d ₆	6.40	<i>g</i>

^a (85JOC5520)

^b (75JCS(P1)31)

^c (78CPB2522)

^d (80JCR(M)514)

^e (69JCS(C)742)

^f (69CJC3677)

^g (89TH1)

range are given by 1-aminobenzimidazole (δ_{NH_2} 4.84) and 2-aminobenzotriazole (8.28 ppm). Interestingly, the signals of the NH_2 groups in the ^1H -NMR spectra of 1-aminopyrrole (69CB3268) and 1-aminoindole (78CPB2522) are recorded at 4.50 and 4.46 ppm, respectively.

Using assignments of the NH_2 group's NMR signals helps to elucidate the course of amination of the tautomeric azoles. Thus, the chemical shift values for 1- and 3-aminoxanthines are recorded over a range of 5.30–5.50 ppm, whereas for 7- and 9-aminoxanthines, the NH_2 signals appear over a range of 6.30–6.40 ppm (81MI1; 89TH1). As a rule signals of each amino group appear distinct in *C,N*-diaminoazoles (73JOC3084; 86S71; 87CPB4031). However, for 1,5-diaminotetrazole, distinction between the signals occurs only below -50°C (6.64 and 6.92 ppm in $\text{DMSO}-d_6$); at room temperature the signals coalesce to one peak of four protons at δ 6.38 (84KGS1683).

Coupling of the NH signal appears as a result of interaction with the α -protons of the *N*-alkyl group in 4-alkylamino-1,2,4-triazoles (88JOC3978).

Somei *et al.* used the chemical shifts in the ^{13}C -NMR spectra of *N*-aminopurines to determine the position of amination (78CPB2522). On the whole, the chemical shifts in the ^{13}C -NMR spectra of *N*-amino- and *N*-alkyl-purines are very similar. This is also true with *N*-aminopyrazoles (88CPB3838), *N*-amino-1,2,3-triazoles (80JHC1127; 89JHC301), and other *N*-aminoazoles [80JCR(M)514]. The ^{13}C -NMR spectra of 1-(*N*-arylideneamino)-1,2,3-triazoles have been investigated (88JHC565; 88JHC1161). Recently, ^{15}N -NMR spectra of some *N*-aminoazoles were reported [90JCS(P)237].

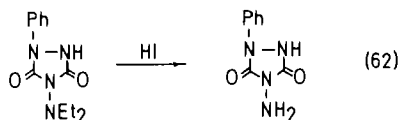
4. Mass Spectra

Mass spectra of *N*-aminoazoles have not been systematically investigated. From numerous isolated data, one can draw the conclusion that the molecular ion for *N*-aminoazoles appears to be a base peak in most cases. The primary fragmentation includes, as a rule, the loss of a fragment with m/z 15 (obviously, NH), and the pseudomolecular ion of the azole without the amino group is formed. Such fragmentation is characteristic, for instance, of almost all *N*-aminopyrazoles (85LA1732) and 9-aminoxanthines (89KGS95). In the mass spectra of 1,3- and 1,5-diaminopyrazoles, the (M-16) peak is observed instead of the (M-15) peak; however, it is not clear which amino group is responsible for the former fragment (86S71). Mass spectra of 1-arylamino-, 1-ureido-, and 1-arylideneamino-1,2,3-triazoles have been investigated in detail (68TL231; 84JHC145; 87JHC1461).

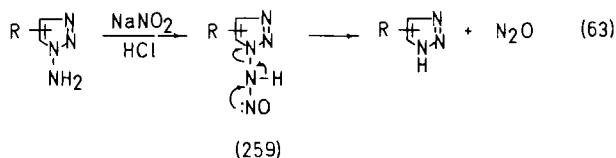
IV. Reactions

A. ELIMINATION OF *N*-AMINO GROUP; ITS USE AS A PROTECTIVE GROUP

The *N*-amino group is strongly attached to the azole nucleus, and most *N*-aminoazoles are not decomposed on refluxing in acidic or alkaline solution. For instance, to separate it from unreacted benzimidazole, 1-aminobenzimidazole can be crystallized from 10–15% alkali. Hydroiodic acid acted on 1-phenyl-4-diethylamino-*s*-triazoline-3,5-dione to eliminate the ethyl groups, but conserved the N—NH₂ bond [Eq. (62)] (01CB2311; 07CB2093).



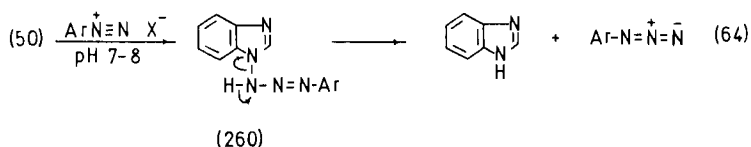
In spite of the evident strength of a N—NH₂ bond, there are some rather mild methods for eliminating the *N*-amino group, especially the action of nitrous acid or nitrogen trioxide on *N*-aminoazoles. This method was discovered by the first investigator of *N*-aminoazoles and was described for 4-amino-1,2,4-triazoles (1888JPR531; 07CB815) and 1-amino-1,2,3-triazoles (04JPR433; 09CB659) as examples. The reaction occurs extremely rapidly and readily even at 0–20°C and is accompanied by the elimination of nitros oxide, obviously, as a result of the decomposition of the labile *N*-nitrosamine **259** [Eq. (63)].



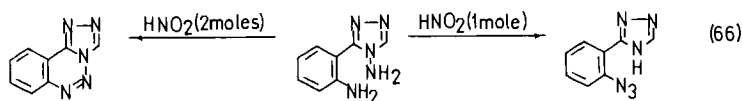
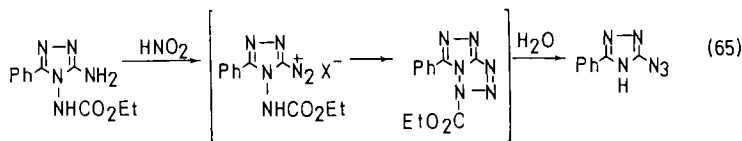
This method was evaluated for all types of *N*-aminoazoles with equally good results. Only if the molecule has the other groups which can react with nitrous acid do secondary reactions occur along with deamination. Thus, under the action of nitrous acid, 1-amino-5-hydrazinotetrazole gives 5-azidotetrazole (31JPR209), 3,4-diamino-*s*-triazol leads to the 1,2,4-triazolyl-3-diazonium salt (53JOC218), and 3-aminothiazoline-2-thiones (57YZ771) and 4-amino-*s*-triazoline-3-thiones (64JOC1174) are converted

to the corresponding disulfides. Sometimes deamination is accompanied by the C-nitrosation of the π -excess heterocycle (54CB1385; 90KGS1517).

As was shown for *N*-aminobenzimidazoles, *N*-aminoazoles are easily deaminated by the action of diazonium salts (79ZOR1108). Unfortunately, this interesting reaction has been poorly investigated so far. Its value lies not so much with deamination but with the formation of aryl azides under mild conditions in high yields. Probably, the intermediates in this reaction are tetrazenes **260** cleaved (probably, via the N-anion) as shown in Eq. (64).

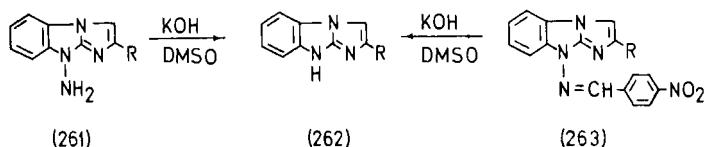


There are examples of intramolecular reactions of this type [Eqs. 65 and 66] [69ZC338; 72JCS(P1)1842].

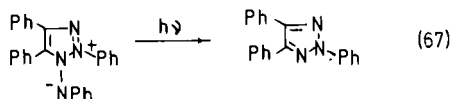


In spite of the stability of *N*-aminoazoles towards aqueous alkali, alkaline solutions in dipolar aprotic solvents often cause the elimination of the *N*-amino group. This process is noticeable in DMF; therefore amination in this solvent is reversible and seldom proceeds in good yield (78CPB2522). Usually, deamination readily occurs in DMSO, which has preparative significance. This was first shown for *N*-aminoindole (78CPB2522) and recently was used to synthesize 2-*tert*-butyl- and 2-aryl-imidazo[1,2-*a*]benzimidazoles (**262**) from the more available amines **261**. Deamination of amine **261** with nitrous acid is complicated by nitrosation at position 3 (90KGS1517).

Another method of eliminating the *N*-amino group is by thermolysis of *N*-arylideneaminoazoles accompanied by elimination of arylcyanide (88KGS1226). The reaction needs rather high temperature, for instance, refluxing nitrobenzene. Because of this, it is often accompanied by side processes. Under considerably milder conditions, the nitrile elimination proceeds by the action of alkali in DMSO. Thus Schiff bases were converted to the compounds **262** at 60–70°C in yields of 75–80% (90KGS1517).

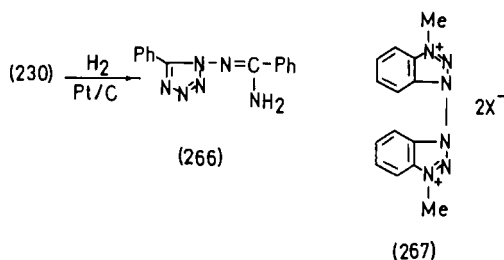
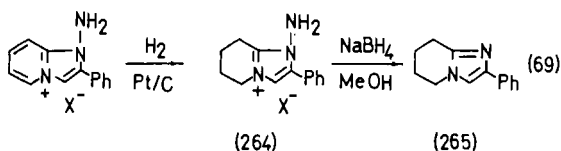
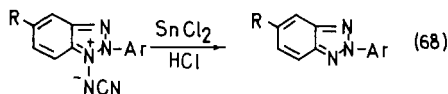


The *N*-amino group in *N*-aminoazolum betaines can be eliminated photochemically [Eq. (67)] (72T3987) (see also 70JPR1112; 71TL3187; 72JPR325). Thermal or acid-catalyzed migration of the *N*-arylamino group to the side chain occurs in similar betaines [83CC627; 89JCS(P1)159].

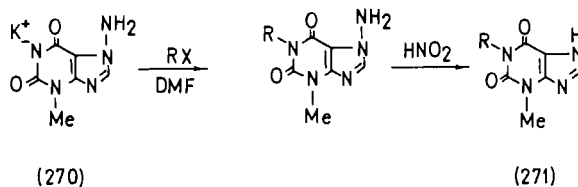
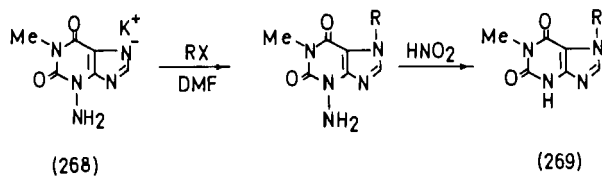


There are examples of reductive cleavage of an N—NH₂ bond [Eqs. (68) and (69)] [64JCS751; 71JCS(C)3280]. However, it should be emphasized that *N*-aminoindole bases are very stable towards the action of reducing agents, and for salts, this process also is not easy. For instance, salt **264** is converted to **265** only in 9% yield on heating with excess sodium borohydride. The internuclear N—N bond is stable also in *N,N'*-diazolyls. Thus, ditetrazolyl **230** is hydrogenated by hydrogen with a partial destruction of one of the hetero-rings and formation of amidine **266**, where a bond between the amine nitrogen atom and the second tetrazole ring remains intact (62CB2546). Raney-nickel converts 2,2'-diindazolyl to indazole (64JOC1150). 1,1-Dibenzotriazolyl is not cleaved by lithium aluminumhydride [80JCR(M)514], but diquatarnary salt **267** gives rise to 1-methylbenzotriazole [85JCS(P1)1209].

The thermodynamic stability of an N—NH₂ bond in combination with the ease of amino group elimination create attractive possibilities to use this group as a protective function. Characteristic examples of this approach include the otherwise nearly inaccessible 1,7-dialkylxanthines **269** (90ZOR1322) and unsymmetrical 1,3-dialkylxanthines **271** (88ZOR1524)

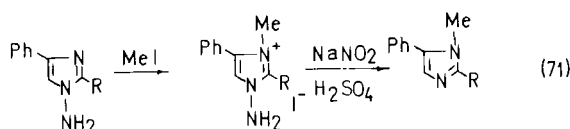
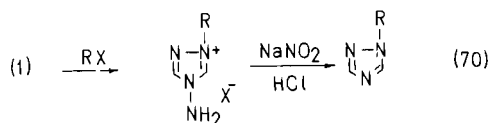


from salts **268** and **270**. The presence of the *N*-amino group in the latter compounds allows one to avoid alkylations at positions 3 and 7 and makes the synthesis extremely effective.



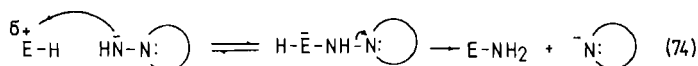
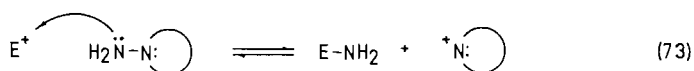
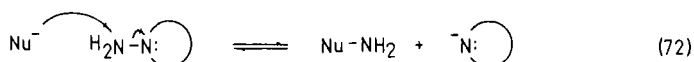
Other examples of the same type include the regioselective synthesis of 1-substituted 1,2,4-triazoles from either 4-aminotriazole (**1**) [Eq. (70)]

(89JOC731) or 4-acetylaminotriazole (72ZC333) and also from 1-methyl-2-R-5-phenylimidazoles by a similar route [Eq. (71)] [72JCS(P1)2927].

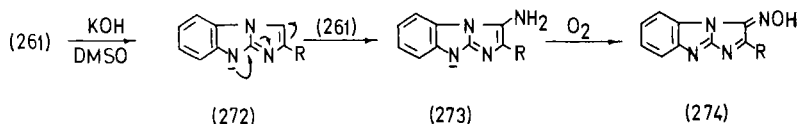


B. *N*-AMINOAZOLES AS AMINATING AGENTS

The reason for using *N*-aminoazoles as the aminating agents is closely connected with the problem of elimination of the amino group and with the mechanism of the N—NH₂ bond cleavage. Theoretically, *N*-aminoazoles can act both as electrophilic [Eq. (72)] and nucleophilic aminating agents, and in the latter case, the reaction may proceed, in principal, with participation of both the neutral amine [Eq. (73)] and the N-anion [Eq. (74)].

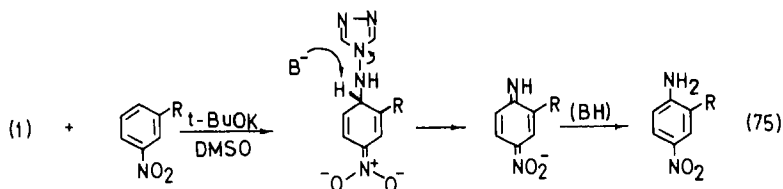


The most natural type seems to be the first reaction, since the *N*-azolyl anions are considered to be good leaving groups. However, there are almost no authentic examples of amination by the mechanism. Probably, by just such a course, *N*-aminoazoles with alkali do deaminate in DMSO. The single instance of electrophile C-amination using an *N*-aminoazole is found in the deamination of 9-aminoimidazo[1,2-*a*]benzimidazoles (**261**) by KOH in DMSO. This reaction gives, along with compounds **262** in a yield of ~15%, 3-nitroso derivatives existing in the oxime form **274** (90KGS1517). Since the anion **272** does not react with hydroxylamine, a reasonable explanation of the formation of **274** consists in transamination of the anion **272** by amine **261** followed by auto-oxidation of the anion of 3-aminoimidazo[1,2-*a*]benzimidazole (**273**). Easy auto-oxidation of the authentic amine **273** under the same conditions supports such an explanation.

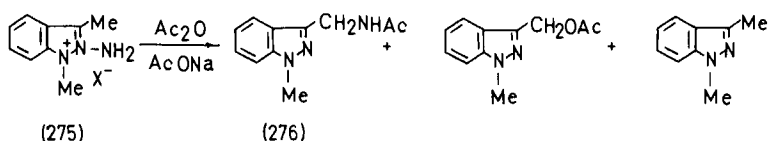


The mechanism of nucleophilic amination presented by Eq. (73) seems very unlikely at first because of the instability of the azolyl cation and the low basicity of the *N*-amino group in *N*-aminoazoles. However, the previously mentioned formation of arylazides from 1-aminobenzimidazole and aryl diazonium salts [Eq. (64)] is concerned, in fact, with such a process. Probably, the course of this reaction is governed also by the elimination of the azolyl fragment as the anion, which is due to the primary deprotonation of tetrazene **260**.

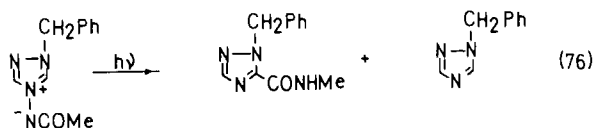
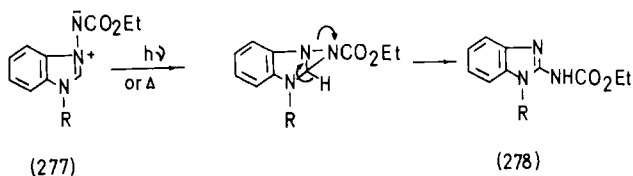
Katrizky and co-workers discovered that 4-amino-1,2,4-triazole in DMSO solution in the presence of potassium *tert*-butoxide is the aminating agent for the π -deficient aromatic substrates, and especially, for nitroarenes (86JOC5039). Thus, nitrobenzene and its 3-substituted derivatives were converted to 2-R-4-nitroanilines. Similarly, 4-alkylamino-1,2,4-triazoles were used to introduce the alkylamino groups in various nitrobenzenes and nitronaphthalenes (88JOC3978). Taking into account the NH-acidity of *N*-aminoazoles (cf. Section III,D), one can assume that under conditions of the reaction, amine **1** is first converted to the anion; i.e., the process proceeds formally by the pathway of Eq. (74). The authors consider this reaction to be a kind of vicarious nucleophilic substitution, since the leaving group (4-triazolyl anion) is eliminated from the nucleophile, but not from the starting substrate [Eq. (75)].



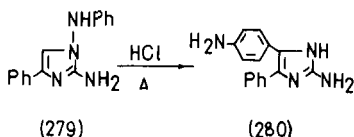
There are several examples of intra- or intermolecular transfer of the *N*-amino group. Thus, 2-aminoindazolium salt (**275**), on treatment with sodium acetate and acetic anhydride, gives 1-methyl-3-acetaminomethylindazole (**276**) in ~10% yield along with 1-methyl-3-acetoxymethylindazole (69%) and 1,3-dimethylindazole (9%) (76CPB2267).



The benzimidazolium *N*-imines (**277**), on thermolysis or photolysis, rearrange to 1-*R*-2-ethoxycarbonylaminobenzimidazoles (**278**) (74JH C781). Photolysis of similar imines in the triazole series proceeds by a slightly different course [Eq. (76)] (70JPR1112; 71TL3187; 72JPR325).



Some examples of a benzidine-type of rearrangement are known for *N*-arylamines which, to some extent, may be considered as analogues of hydrazo compounds. Thus, 1-anilinoimidazole (**279**), on heating in concentrated hydroxyloric acid, is transformed to 4(5)-*p*-aminophenyl derivative (**280**) (70ZC289).



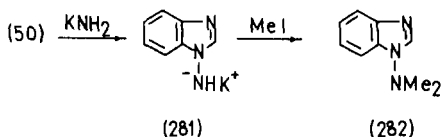
On the whole, the aminating ability of *N*-aminoazoles has been insufficiently investigated, and many problems on both the synthetic and theoretical level await solution. A special interest is the search for a novel aminating agent based on *N*-aminoazoles. In this reaction, *N*-aminoazolium salts have the most promise, since these compounds display a higher ability to lose their *N*-amino group.

C. SUBSTITUTION OF HYDROGEN ATOMS IN AN N-AMINO GROUP

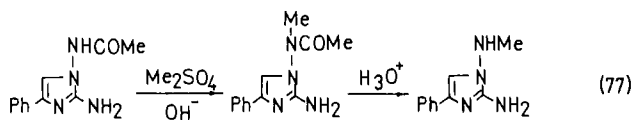
1. Alkylation and Arylation

There are surprisingly few papers on the alkylation of the *N*-amino group in *N*-aminoazoles, in spite of the simplicity and synthetic importance of this reaction. Due to the low basicity of the amino group under neutral conditions, *N*-aminoazoles, namely, 4-amino-1,2,4-triazoles (71JPR795; 89JOC731), *N*-aminoimidazoles [72JCS(P1)2927], *N*-aminobenzimidazoles [73JCS(P1)842; 80KGS814; 83KGS256], and *N*-aminonaphtho[2,3-*d*]imidazoles (06JPR545) are alkylated and aminated (89S269; 89IZV2654) only at the ring nitrogen atom affording the corresponding *N*-aminoazolium or *N,N'*-diaminoazolium salts. The single known exception is 7-aminotheophylline (84), which, on heating with excess methyl iodide in a sealed ampoule, gives 7-dimethylaminotheophylline in 25% yield (89KGS221).

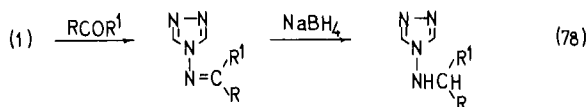
Evidently, for effective alkylation, the *N*-amino group should be ionized. It is the anion of 1-aminobenzimidazole (281) generated by the action of KNH_2 in liquid ammonia that is alkylated by excess methyl iodide to give 1-dimethylaminobenzimidazole (282) in a yield of 52% (89KGS221). The analogous methylation of the amino group was described for 1-amino-3,5-diphenyl-1,2,4-triazole, but *n*-butyl lithium in tetrahydrofuran (THF) was used as a base instead of potassium amide [84JCS(P1)2779].



To obtain monoalkyl derivatives, sodium salts of *N*-aryl- [71JCS(B)1648] and *N*-acylaminoazoles are alkylated, then the acyl group is removed. 1-Alkylamino derivatives of 6-chlorobenzimidazole (73CC41) and 2-amino-4-phenylimidazole (67CB3418) were thus obtained [Eq. (77)].



In a series of papers, *N*-alkylaminoazoles have been synthesized by reduction of the corresponding Schiff bases with the use of sodium borohydride or lithium aluminium hydride. Thus, for instance 4-alkylamino-1,2,4-triazoles [Eq. (78)] (88JOC3978), 3- and 9-benzylaminopurines (78CPB2522), 7-benzylaminotheophylline (81M11), 1-benzylamino-2-aminobenzimidazole (89KGS209), and 1-alkylaminobenzimidazolones (85JHC1089) were obtained. However, on reduction of the Schiff bases formed from 1-amino-2-alkylthioimidazoles with zinc in acetic acid, cleavage of the N—N bond was observed (72CL617; 78BCJ1846).



Anions of oxo and thio derivatives of *N*-aminoazoles are alkylated at the ring nitrogen atom and at the sulfur atom, respectively (c.f., 60LA135; 61ZN767; 84JCS1769).

Only a single patent reports arylation of *N*-aminoazoles. 2-(*o*-Nitrophenyl)aminobenzotriazole was obtained on heating 2-aminobenzotriazole with *o*-nitrofluorobenzene in DMF in the presence of anhydrous soda (65USP3184471). An attempt to carry out such a reaction for 1-aminobenzotriazole failed, probably because of the poor NH-acidity of this compound.

2. Acylation

N-Acylation is one of the most important synthetic methods in the chemistry of *N*-aminoazoles, and is widely used in various heterocyclizations as well to protect the amino group. There are numerous papers devoted to acylation of practically all types of *N*-aminoazoles, with the exception of *N*-aminopyrazole. As acylating agents, carboxylic acids

[alone or in the presence of polyphosphoric acid (PPA)], their anhydrides, and their chlorides (usually in the presence of alkali or in pyridine) were used. For instance, 1-aminobenzimidazoles, on refluxing in formic or acetic acid, are converted to *N*-formyl- and *N*-acetyl derivatives in high yield (63JOC736).

Transacylation occurs when 1-acetylamino- or 1-propionylamino-benzimidazoles are heated with excess formic acid, giving 1-formylaminobenzimidazoles [73JCS(P1)842]. Refluxing 1-aminobenzimidazoles in acetic anhydride leads to the formation of 1-diacetylamino-benzimidazoles (80KGS814). There are also some data on acylation of 7-aminotheophiline with carboxylic acids in PPA (87KGS1398) and acyl chlorides in pyridine (81MI1); of 1-amino-*v*-triazoles with acyl chlorides in alkaline medium (09CB659), phthalic anhydride [73JCS(P1)555], and arylsulfonyl chlorides (61CB3260); of 1-amino-*s*-triazoles with acetic anhydride (63CB2750); and of 4-amino-*s*-triazoles with carboxylic acids (09CB2715), anhydrides (69JPR897) and arylsulfonyl chlorides (51JA2558; 84JCG797).

1-Aminotetrazole, under the action of tosyl chloride in alkaline solution, yields 1-tosylaminotetrazole; however, on carrying out the same reaction with chlorides and anhydrides of carboxylic acids, a characteristic reaction for tetrazoles—transformation to 2-acylamino-1,3,4-oxadiazoles—took place (60CB850).

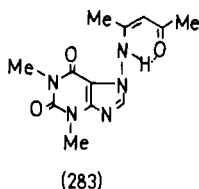
Sodium salts of 1-arylamino-*v*-triazoles (**124**) are acylated at low temperature at the oxygen atom, affording isoimides **122**. The latter compounds, as already noted, are isomerized on heating to 1-(*N,N*-diarylamino)-*v*-triazoles (78JHC1255; 84JHC1653).

It is also possible to acylate *N*-aminoazolum salts, which was demonstrated for 4-amino-*s*-triazolium (69JPR897), 3-aminothiazolium (74CPB482), *N*-aminoimidazolium and *N*-aminobenzimidazolium salts (74JHC781).

In *N,C*-diaminoazoles, such as 1,5-diaminotetrazole (69CJC3677) or 7,8-diaminotheophilline (87CPB4031, 87KGS1398), the *N*-amino group is first acylated. However, on using excess acylating agent and more severe conditions, one can also obtain di-, tri-, and tetraacyl derivatives. The mercapto derivatives of *N*-aminoazoles, for example, 1-aminoimidazoline-2-thione (63LA113) or 4-amino-*s*-triazoline-3-thiones (86JHC1451), are acylated on the *N*-amino group. The acylation of 1-aminoimidazole-2-ones also proceeds on the amino group (64CB1031). For elimination of the *N*-acyl group, hydrolysis in acids, such as hydrochloric, hydrobromic or sulfuric, is usually applied. For removing the phthaloyl protecting group, hydrazine hydrate is used (72JOC2351; 73CC819). In *N,N*-ditosylaminoazoles, selective removal of one tosyl group is possible under the action of sodium methylate [69JCS(C)769].

3. Schiff Base Formation

The Schiff bases (they may be also considered as specific hydrazones) play a great role in the chemistry of *N*-aminoazoles. In most cases, these compounds are obtained by cyclization of a suitable acyclic compound or by interaction of an *N*-aminoazole with carbonyl compounds: aldehydes, ketones, or their acetals. Usually the reaction is carried out on heating components in acetic acid or in alcohol in the presence of catalytic amounts of a mineral acid. The use of β -dicarbonyl compounds requires more drastic conditions. Thus, 1-aminobenzimidazoles (83KGS386) or 7-aminotheophiline (87KGS1551) reacts with acetylacetone at 175°C in the presence of anhydrous zinc chloride, yielding hydrazones of type **283**.



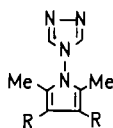
As for *N,C*-diaminoazoles, such as 1,5-diaminoimidazoles (61JCS3816), 7,8-diaminotheophiline (87CPB4031, 87KGS1398) or 3,4-diamino-*s*-triazoles (34JPR193; 65JHC98; 85MI2; 86MI1; 89JHC1077), reaction occurs only on the *N*-amino group, even in the presence of excess aldehyde. Since formation of Schiff bases is described in almost every paper devoted to *N*-aminoazoles, we cite in this chapter only selected references on the main types of *N*-amino azoles: pyrazoles [86JCS(P1)1249], indazoles [75JCS(P1)31], imidazoles (82S592), benzimidazoles (55JCS2326; 63JOC736; 81KGS1497), 1,2,3-triazoles (09CB659; 87JHC1461), benzotriazoles [69JCS(C)742], 1,2,4-triazoles (09CB2715; 63CB2750; 88JOC3978), 9-aminopurines (60JA4592; 78CPB2522), 7-aminoxanthines (81MI1; 87KGS1551), tetrazoles (60CB850), and thiazoles (59JPR265).

Schiff bases are readily hydrolyzed on heating with acids; however, occasionally, due to their insolubility in acidic medium, hydrolysis can be carried out only in aqueous alkali (87KGS836).

4. Miscellaneous Reactions

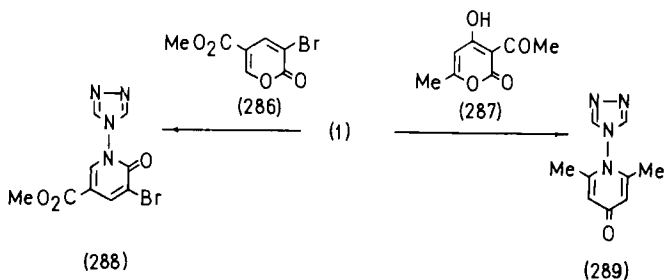
N-Aminoazoles react with 1,4- and 1,5-dicarbonyl compounds and with their masked analogues to afford various *N*-hetarylazoles. Thus, at the beginning of the century, Bülow discovered that 4-amino-1,2,4-triazole, on interaction with acetonylacetone and esters of diacetyl succinic acid,

gives rise to 4-(pyrrolyl-1)-1,2,4-triazoles (**284**) (06CB2618, 06CB4106; 09CB2487). Later, these data were supported (74TL4123), and the method was applied to the synthesis of *N*-pyrrolyl derivatives of benzotriazole, benzimidazole, and 9-aminopurines (78CPB2522). For synthesizing *N*-pyrrolylazoles without substituents in the pyrrole ring, 2,5-diethoxytetrahydrofuran is used [74TL4123; 80JCR(M)514; 85JCS(P1)1209]. *N*-Aminoazoles, for instance, 4-amino-1,2,4-triazole (74TL4123) and 1-aminopyrazole [85JCS(P1)1209; 85TL5485], react with pyrylium salts to yield *N*-azolylpyridinium salts of type **285**.

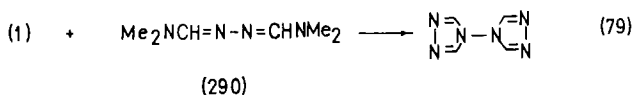
(284) R=H, CO₂Me

(285) R=Me, Ph

The reaction of 4-amino-1,2,4-triazole with α -pyrone derivatives **286** and **287** leads to *N*-triazolylpyridones **288** and **289** [09CB1990; 85JCS(P1)1209]. However, it was not possible to obtain such compounds using 1-aminopyrazole and 1-aminobenzimidazole [85JCS(P1)1209].

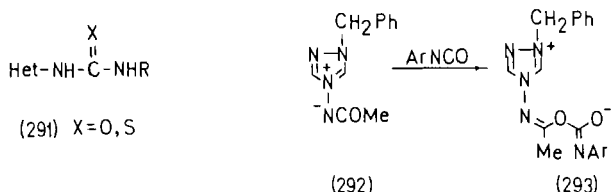


N,N-Dimethylformamide azine (**290**) is a suitable synthon for obtaining *N*-triazolylazoles from *N*-aminoazoles [Eq. (79)] [80JCR(M)514; 85JCS(P1)1209].

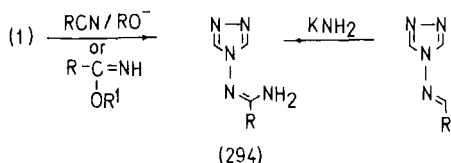


Like all amines, *N*-aminoazoles are easily added to aryl isocyanates and aryl isothiocyanates, yielding *N*-ureido- or *N*-thioureidoazoles **291**. To

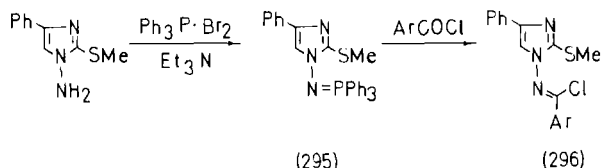
obtain compounds **291** ($X = O$), N,N' -disubstituted ureas can be used instead of isocyanates (71JPR795). Such reactions were carried out for many N -aminoazoles: 4-amino-1,2,4-triazole (09CB2715; 71JPR795), 1-aminotetrazole (60CB850), and 4-aminoimidazoles (64CB1031). Interestingly, N -acylaminobetaines **292** take part in such reactions with participation of the oxygen, but not the nitrogen atom, affording compounds **293** (71JPR795).



N -Aminoazoles, for instance **1**, react with nitriles or iminoesters to yield amidines **294** (69JPR477; 71JPR768). The latter compounds were also obtained on amination of the Schiff bases with potassium amide in liquid ammonia (70JPR669).

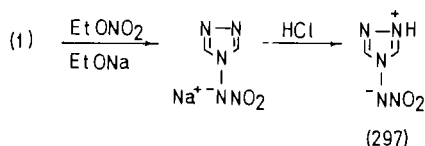


N -Aminoazoles react with the $\text{Ph}_3\text{P} \cdot \text{Br}_2$ complex in the presence of mild bases to give phosphazo compounds **295**, which are transformed to α -chlorohydrazones **296** under the action of acylchlorides (88H1935).



The N -nitration of 4-amino-1,2,4-triazole, 1-aminobenzimidazole, N -aminobenzotriazole [73JCS(P1)2624] and 1,3-diamino-1,2,3-triazolium salts (89IZV2654) have been reported. The nitramine products exist in the

betaine form **297**. Their stability stands in contrast to the unstable *N*-nitrosoaminoazoles **259**.



Another way to introduce substituents at the *N*-amino group is via oxidation to an *N*-nitrene. Such reactions are discussed in Section IV,D.

D. OXIDATION

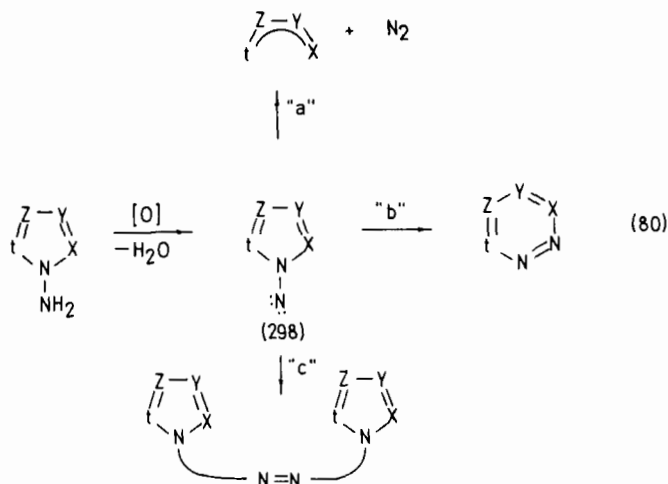
1. General Considerations and Mechanistic Aspects

Contrary to the majority of other reactions of *N*-aminoazoles, oxidation reactions only began to be studied much later, approximately from the 1960s. Since that time, interest has grown, and presently they represent one of the most intriguing and synthetically useful types of *N*-aminoazole conversions. With the help of these reactions, one can effectively generate cycloalkynes and arynes, synthesize the difficult-to-obtain 1,2,3- and 1,2,4-triazines, *N,N'*-azoazoles, and other important compounds.

Oxidation reactions of *N*-aminoazoles can be divided into five types:

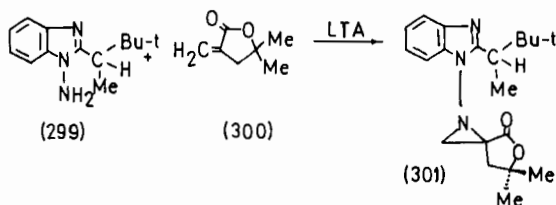
- (1) Fragmentation accompanied by nitrogen molecule ejection and formation of a ring-opened intermediate [pathway a, Eq. (80)]
- (2) Ring enlargement with introduction of the amine nitrogen atom into the ring (pathway b)
- (3) Dimerization leading to *N,N'*-azoazoles (tetrazenes) (pathway c)
- (4) Elimination of the *N*-amino group
- (5) Other reactions specific to individual *N*-aminoazoles.

Although the oxidation pathway is determined mainly by the nature of the azole nucleus, the conditions and the oxidants also have great significance. In the first experiments, the oxidant most used was lead tetraacetate. It still dominates, but many other oxidants have appeared, and they frequently give better results, for instance, nickel peroxide, manganese dioxide, potassium periodide, bromine water, and *N*-bromosuccinimide. Reactions with LTA are usually carried out in absolute methylene chloride at about 0–20°C, and for neutralization of the released

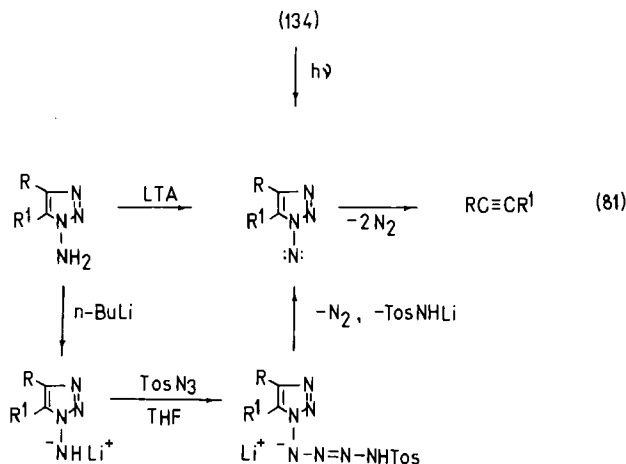


acetic acid, one can sometimes use calcium oxide. In other cases, the presence of acid is desirable, and acid is even added to the reaction mixture, for instance, to obtain 1,2,3-triazines from 1-aminopyrazoles (85JOC5520). Oxidation often proceeds by several parallel pathways.

Besides the synthetic significance, a second stimulus to investigate oxidation reactions of *N*-aminoazoles is to study the as yet unclear mechanism (84M11). The center of all the arguments and discussions is the question of whether *N*-nitrene **298** is formed as an intermediate or does some other pathway occur? In spite of the absence of direct proof for *N*-nitrene formation, almost all investigators support on the basis of some oblique features the participation of such intermediates. Thus, *N*-nitrenes can be captured by traps, such as alkenes (styrene, methylacrylate, etc.) or DMSO (88M1041). In the first case, the corresponding aziridines are the products of reaction; the latter case yields sulfoxymines. For instance, on oxidation of the chiral *N*-aminobenzimidazole **299** in the presence of alkene **300**, aziridine **301** is formed as the only stereoisomer with 69% yield [86CC832; 87JCS(P1)2787]. The high stereospecificity of such conversion is evidence that *N*-nitrene reacts in a singlet state.



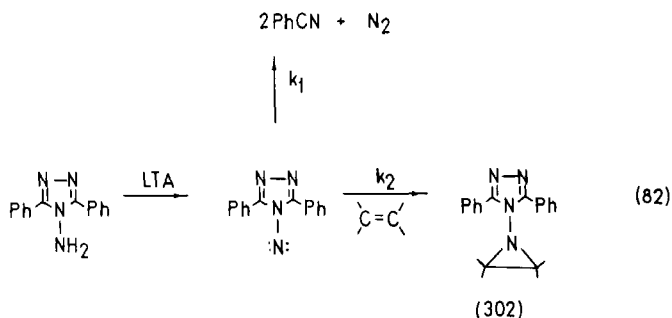
Other evidence to support nitrene formation is the identity of the reaction products obtained when nitrenes are generated by independent methods. For instance, *N*-nitrenes of 1,2,3-triazoles can be generated by oxidation of 1-amino-*v*-triazoles (88M1041), on photolysis of their potassium tosylates² (**134**) (64AG144), or by decomposition of unstable lithium salts of 1-(1,2,3-triazole-1-yl)-4-*p*-tolylsulfonyl-tetrazenes [72JCS(P1)1315] [Eq. (81)]. In all three cases, the corresponding acetylenes are formed in good yield as the result of *N*-nitrene fragmentation.



German chemists investigated the kinetics of the oxidation of 4-amino-3,5-diphenyl-1,2,4-triazole in the presence of substituted styrenes and other alkenes (74TL2945). The rates of the two competing reactions—fragmentation leading to benzonitrile and formation of aziridine **302** [Eq. (82)]—were measured. On introduction of donor groups (*p*-Me, *p*-OMe, etc.) into the molecule of styrene, the k_2 value increased relative to k_1 . *trans*-Alkenes give aziridines more easily than *cis*-alkenes. Such results represent more indirect evidence for *N*-nitrene generation because *N*-nitrenes are electron deficient.

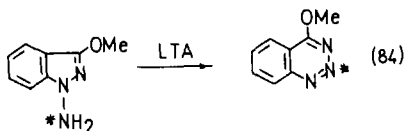
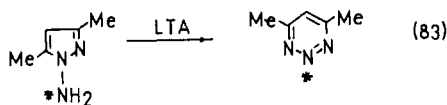
Ring enlargement requiring intramolecular attack by the nitrene nitrogen atom on a neighboring ring atom is especially characteristic of *N*-

² Potassium tosylates of *N*-aminoazoles including **134**, tosylates of *N*-aminobenzotriazoles [72JCS(P1)1315], and *N*-aminopyrroles (63JA1944; 70TL3851) are stable on thermolysis unlike alkylhydrazine tosylates. This is because *N*-azolylnitrenes are resonance stabilized less than alkylaminonitrenes due to delocalization of the nitrogen electron pair into the aromatic ring.



aminoazoles, which have rings with relatively high π -electron density (1-aminopyrazoles, *N*-aminoindazoles, 7-aminoxanthines). At the same time, this reaction is very rare for *N*-amino derivatives of the more electron-deficient triazoles and condensed imidazoles. However, few things are so simple. For instance, oxidation of 1-amino-2,5-diphenylpyrrole, which according to this point of view should easily give 3,6-diphenylpyridazine, gives the corresponding 1,1'-azopyrrole, which decomposes at 200°C to yield 2,5-diphenylpyrrole. Similarly, oxidation of *N*-aminocarbazole with LTA gives carbazole (73%) (70TL3851).

It was established that on ring enlargement the nitrene nitrogen atom can attack not only a neighboring carbon atom, but also a nitrogen atom even more easily [86JCS(P1)1249]. Oxidation of 1-amino-3,5-dimethylpyrazole and 1-amino-3-methoxyindazole with the *N*-amino group ^{15}N enriched led to 1,2,3-triazines containing the label only in position 2 [Eqs. (83) and (84)]. It would also be interesting to carry out similar investigations for such easily ring-enlarged compounds as 1,2-diaminobenzimidazole or 7-aminotheophiline.



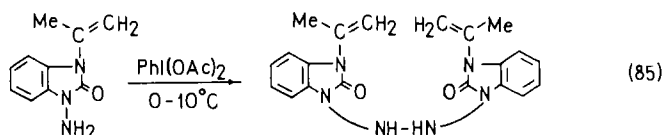
Boulton and co-workers [86JCS(P1)1249] suggested three distinct classes of *N*-nitrenes:

- (1) Hard nitrenes without a tendency to fragment or to ring enlarge, but inclined to be captured by traps.
- (2) Fragmenting nitrenes [pathway a, Eq. (80)]; for these, dimerization yielding tetrazenes is a rather characteristic side reaction. They can also be captured by traps.
- (3) Rearranging nitrenes. These rapidly enlarge the ring and are seldom captured by traps.

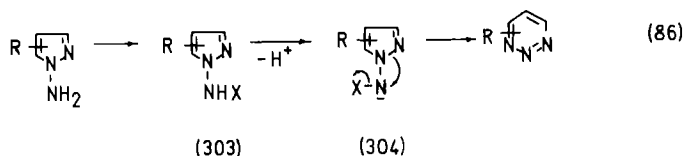
In spite of the usefulness of this classification, its rather approximate and even contradictory character should be emphasized. Thus, nitrenes generated from 4-amino-*s*-triazoles and 1-amino-*v*-triazoles easily undergo a fragmentation; but whereas the former compounds readily yield aziridines or sulfoximines, the latter ones are practically never captured by traps (88M1041). By analogy, 1-aminopyrazoles give 1,2,3-triazines on oxidation, i.e., they belong to the third type. At the same time, 1,1'-azopyrazoles are formed in noticeable amounts which are typical for nitrenes of the second class. However, the most serious problem connected with the nitrene classification is concerned with the multipath nature of the oxidation reaction mechanism.

Clearly, in many cases where the formation of *N*-nitrenes has been postulated as intermediates, the process really proceeds by an alternate non-nitrene pathway. For example, the mechanism of such an apparently simple reaction as the formation of *N,N'*-diazoles may be presented as (1) the result of dimerization of two nitrene particles; (2) interaction of the *N*-nitrene with the starting amine affording a tetrazane followed by its oxidation ($\text{R}-\ddot{\text{N}} + \text{R}-\text{NH}_2 \rightarrow \text{R}-\text{NH}-\text{NH}-\text{R} \xrightarrow{[O]} \text{R}-\text{N}=\text{N}-\text{R}$), and (3) dimerization of two radicals $\text{R}-\dot{\text{N}}\text{H}$, which also yields the tetrazane and then the azo compound.

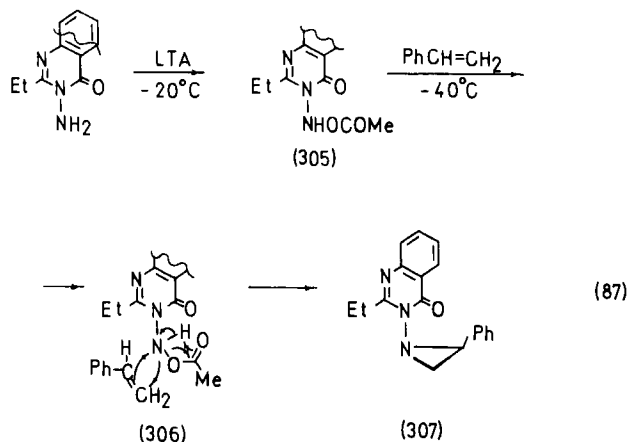
Tetrazanes could be obtained on cautious oxidation of *N*-amino derivatives of some six- and five-membered heterocycles with phenyliodo diacetate [Eq. (85)] (71CC800). The tetrazane products are very unstable and easily decompose with nitrogen elimination and formation of deaminated NH-heterocycles. Probably, on oxidation of *N*-aminoazoles, deamination occurs via the tetrazane formation.



Japanese chemists, on investigation of *N*-aminopyrazole oxidation, assumed that the formation of 1,2,3-triazines may be presented via intermediates **303** and **304** [Eq. (86)] based on a nitrene mechanism (88CPB3838).



Compounds of type **303** were isolated by Atkinson and Kelly on cautious oxidation of 3-amino-2-ethylquinazolone-4 [Eq. (87)] (87CC1362). *N*-Acetoxyamino derivative **305** is stable only at temperatures below 0°C, and at -40°C it reacts with styrene to give aziridine **307**, supposedly via intermediate **306**. These data were interpreted as a proof of the possibility of forming aziridines without *N*-nitrene participation. Notice, however, that in principal there is no great difference between the nitrene mechanism and mechanisms presented in Eqs. (86) and (87), since if elimination of X from **304** and of MeCO₂⁻ from **305** is a little ahead of the following reaction, then, in fact, the masked nitrene mechanism is described.

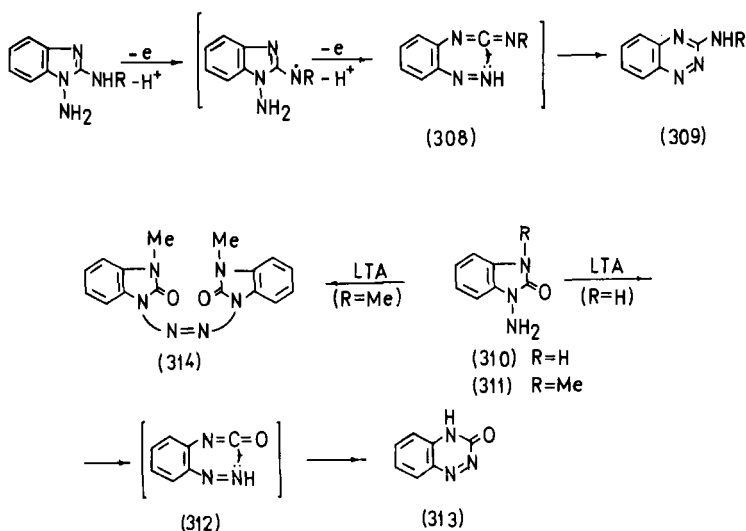


Indirect data suggest that ring enlargement sometimes occurs by a mechanism not involving an *N*-nitrene or by a masked modification, as shown in Eq. (86). Thus, a paradox in *N*-aminobenzimidazole chemistry is that whereas 1,2-diaminobenzimidazole and its Bz-substituted derivatives give, on oxidation, 3-aminobenzo-1,2,4-triazines (**309**, R = H) in high yield (77JOC542), 1-amino-2-alkylaminobenzimidazoles under the same condi-

tions are mainly converted to the corresponding 1,1'-azobenzimidazoles, and yield of the 3-alkylaminobenzotriazines (**309**, R = Alk) is not greater than 30% (89KGS1486). 1-Amino-2-dialkylaminobenzimidazoles, on oxidation, give only unstable tetrazenes and do not form even a trace of 3-dialkylaminobenzotriazines.

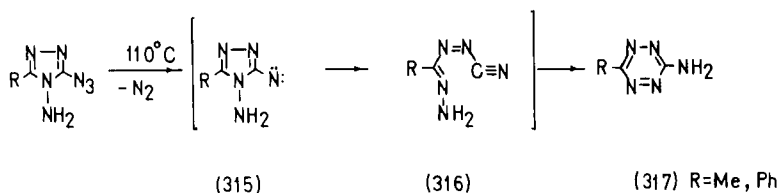
Structure changes also dramatically affect the oxidation pathway of 1-aminobenzimidazolones. Unsubstituted 1-aminobenzimidazolone (**310**) under the action of lead tetraacetate is converted to benzotriazinone **313**, whereas the only product of oxidation of 1-amino-3-methylbenzimidazolone (**311**) is tetrazene **314** (89KGS1486).

It is difficult to assume that *N*-nitrenes generated from compounds **310** and **311** or from 1,2-diaminobenzimidazole will have a different behavior. The only structural difference between these *N*-aminobenzimidazoles undergoing the ring enlargement is the presence of the mobile hydrogen atom in the second functional group. Hence, the mechanism of benzotriazine formation may involve oxidative elimination of the hydrogen atom from the *C*-amino group, forming diazene intermediates **308** and **312**, which undergo recyclization (89KGS1486). This mechanism is supported by data on electrochemical oxidation of *N*-aminobenzimidazoles and by the higher NH-acidity of the 2-amino group in comparison with the *N*-amino group (89KGS221).



The diazene mechanism was accepted by Japanese chemists for the oxidation of 1,2-diaminoimidazoles, but only as an explanation of side-product formation (78JOC2693). The possibility of a non-*N*-nitrene path-

way of azole ring enlargement is supported by the synthesis of 3-amino-*s*-tetrazines (**317**) with 95% yield on thermolysis of 4-amino-3-azido-1,2,4-triazoles. This reaction probably also proceeds via the diazene intermediate **316** formed from *C*-nitrene **315** (66TL5369).



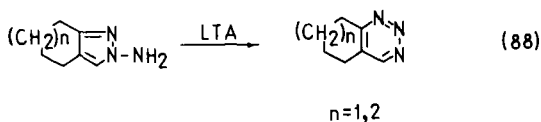
2. *N*-Aminopyrazoles

Oxidation of *N*-aminopyrazoles is the best synthetic method for producing 1,2,3-triazines and is the only route to producing unsubstituted 1,2,3-triazine. The yield of triazine and the formation of side products strongly depend on the structure of the *N*-aminopyrazole and on the oxidant used. One can use lead tetraacetate [80CC1182; 85JOC5520, 85LA1732; 86H907, 86JCS(P1)1249], nickel peroxide (81CC1174; 85JOC5520, 85LA1732), manganese and lead dioxides (85JOC5520), halogens, interhalogens, *N*-chloro- and *N*-bromosuccinimides (88CPB3838), and sodium and potassium periodates (89H1809).

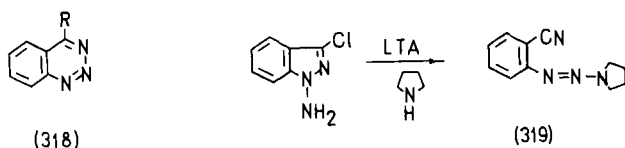
For the oxidation of unsubstituted 1-aminopyrazole, the highest yield (46%) of 1,2,3-triazine is obtained with sodium periodate, which also provides high yields (82–93%) for other triazines (89H1809). 1,2,3-Triazine can be obtained in ~20% yield on oxidation of *N*-aminopyrazole with nickel peroxide or lead dioxide in methylene chloride in the presence of acetic or trifluoroacetic acid (85JOC5520, 85LA1732); however, these results are not always reproducible [86JCS(P1)1249]. As side products, *cis*- and *trans*-isomers of *N,N'*-azopyrazoles are often isolated in yields of 35–45%.

Lead tetraacetate gives only traces of unsubstituted 1,2,3-triazine, whereas di- and trisubstituted *N*-aminopyrazoles are converted to triazines in yields of 30–75% by this oxidant [Eq. (88)] (86H907) (cf. 85JOC5520, 85LA1732). The only exception is 1-amino-3,4,5-triphenylpyrazole reacting with LTA to afford a mixture of 3,4,5-triphenylpyrazole (63%) and tetrazene (18%) [86JCS(P1)1249]. With halogenating reagents, *N*-aminopyrazoles react differently: chlorine causes deep degradation; iodine leads to 1,2,3-triazines in small or moderate yield; bromine usually bromi-

nates the pyrazole ring, yielding 1-amino-4-bromopyrazoles. The use of *N*-bromo- and *N*-chlorosuccinimides gives complex mixtures of products (88CPB3838).



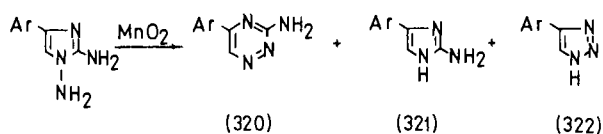
Both 1- and 2-aminoindazoles are oxidized with LTA to afford benzo-1,2,3-triazines **318** in good yield. Only for unsubstituted benzo-1,2,3-triazine (**318**, R = H) is the yield less than 20%, due to its instability towards nucleophiles [71CC828; 75JCS(P1)31]. 1-Amino-3-chloroindazole behaves anomalously because it is converted by the action of LTA in pyrrolidine to triazene **319** (83CC1344). Another rather unusual reaction is the formation of 2,2'-di-indazolyl (69% yield) on refluxing 2-aminoindazole with mercuric oxide in butyl alcohol (72JOC2351). An attempt to carry out the analogous conversion of 1-aminobenzimidazole failed [81JCS(P1)403].



N-Amino derivatives of condensed pyrazoles **26**, **27**, **29**, and **31** are readily oxidized with LTA to the corresponding triazines [75JCS(P1)31, 75JCS(P1)1747].

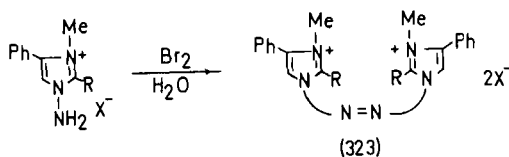
3. *N*-Aminoimidazoles

There are few data on the oxidation of noncondensed *N*-aminoazoles. Manganese dioxide converts 1,2-diamino-4-arylimidazoles into complex mixtures of the corresponding 3-amino-1,2,4-triazines (**320**), 2-aminoimidazoles (**321**), 1,2,3-triazoles (**322**), and some open-chain compounds (76TL903; 78JOC2693). The yield of 1,2,4-triazines **320** is usually less than 25%, but on oxidation of 1,2-diamino-4,5-diphenylimidazole, it increases to 62%. It is assumed that triazines **320** are formed via a nitrene mechanism, whereas for 1,2,3-triazoles **322**, the diazene mechanism is postulated. However, the latter may also apply to compounds **320**.



Unsubstituted 1-aminobenzimidazole yields about 5% of 1,1'-azobenzimidazole under the action of LTA (86KGS999; 89KGS1486) or nitronium tetrafluoroborate [73JCS(P1)2624]. If LTA is used, 1-acetylbenzimidazole is formed as a side product. The yield of 1,1'-azobenzimidazole can be increased to 25% by the use of bromine water as an oxidant (89KGS1486). The formation of tetrazenes proceeds especially readily on oxidation of 2-methyl-, 2-phenyl-, and 2-chloro-1-aminobenzimidazoles (89KGS1486). In the latter case, the tetrazenes yield reaches 58%, a record for *N*-aminoazoles. Oxidation of 1,2-diaminobenzimidazoles was discussed in Section IV,D,1. In the presence of alkenes, *N*-aminobenzimidazoles are oxidized to give 1-aziridinylbenzimidazoles [86CC832; 87CC456, 87JCS(P1)2787].

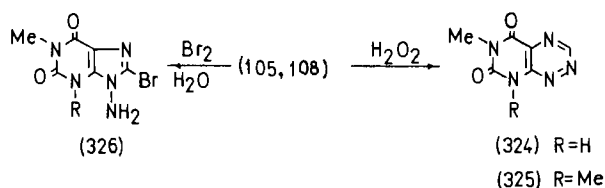
Glover and co-workers synthesized tetrazenium salts **323** in 60–78% yield by the action of bromine water on 1-amino-3-methylimidazolium salts [72JCS(P1)2927]. Similarly obtained were the salts of 1,1'-azobenzimidazolium [73JCS(P1)842], 1,1'-azoimidazo[1,2-*a*]pyridinium [71JCS-(C)3280], 1,1'-azoimidazo[1,2-*a*]pyrimidinium [77JCS(P1)78], and 7,7'-azoimidazo[2,1-*b*]thiazolium [74JCS(P1)1137]. However, 1-phenyl-2-aminoimidazo[1,5-*a*]pyridinium salt is deaminated by bromine, and LTA in acetic acid converts the salt into 1-phenyl-2-acetylaminimidazo[1,5-*a*]pyridine-3-one [79JCS(P1)1833].



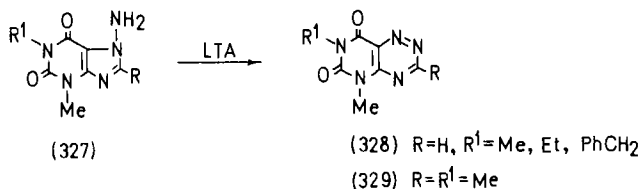
4. *N*-Aminopurines

In a series of papers, oxidations of 7- and 9-aminoxanthines were investigated. 1-Methyl-9-aminoxanthine (**105**) and 9-aminotheophiline (**108**) are inert towards LTA and many other oxidants. Only by the use of 30% hydrogen peroxide were the antibiotics reumicine (**324**) and phervenuline (**325**) obtained in a yield of about 40%. Bromine in water or in acetic acid

converts amines **105** and **108** into 8-bromo-substituted derivatives **326** in almost quantitative yield (89KGS95).

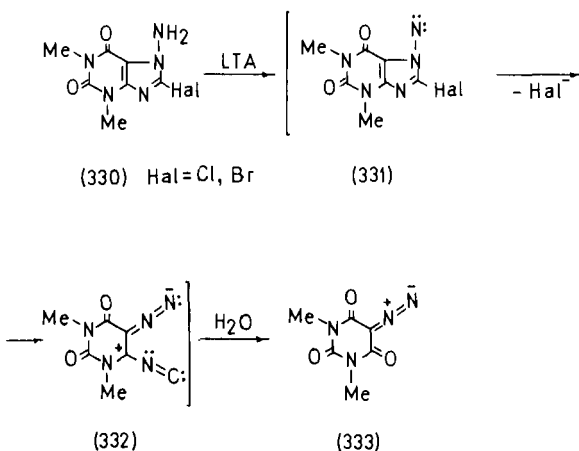


Contrary to 9-aminoxanthines, 7-aminoxanthines **327** (R = H) are readily oxidized with LTA and other oxidants ($\text{Br}_2/\text{H}_2\text{O}$, $\text{HNO}_3/\text{H}_2\text{SO}_4$, $\text{KClO}_3/\text{H}_2\text{SO}_4$, HIO_4 , $\text{KMnO}_4/\text{H}_2\text{SO}_4$, and H_2O_2) to give isophervenules in high yield. This method synthesizes these important compounds best (81MI1; 83KGS1564; 87KGS1555; 89KGS95, 89TH1). Slight modifications of the reaction conditions sometimes change its direction. Thus, in contrast to bromine water, bromine in acetic acid does not oxidize, but brominates 7-aminotheophiline. Similarly, nitric acid in acetic acid nitrates 7-aminotheophiline at position 8 (89KGS95).

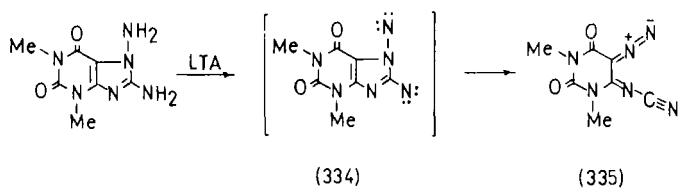


The presence of substituents at position 8 strongly affects the ease and direction of oxidation of 7-aminotheophelines. Thus, 7-amino-1,3,8-trimethylxanthine and LTA gives only 27% 6-azalumazine **329** (87KGS1555). It was impossible to oxidize 7-amino-8-nitrotheophiline. The behavior of 7-amino-8-halogenotheophelines (**330**) is very interesting (83KGS1564). On oxidation they unexpectedly give 1,3-dimethyldiazobarbituric acid (**333**). The reaction probably proceeds via nitrene **331**, undergoing stabilization on elimination of the Hal^- anion with the formation of intermediate **332** in which the isonitrile group is substituted by the nucleophilic action of water.

Similarly, on oxidation, 7,8-diaminotheophiline yields the cyanoimino derivative of diazobarbituric acid (**335**) (89KGS1486). The formation of **335** is formally on isomerization of dinitrene **334**. 3-Aminoisophervenule (**329**, R = NH_2), another potential precursor of the compound **335**, is not

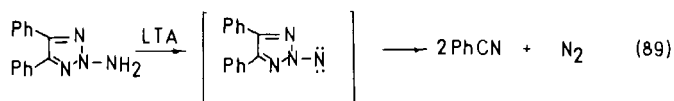


on the reaction coordinate, since it is inert towards LTA. Isolation of **335** strongly supports the diazene mechanism of ring enlargement on oxidation of 1,2-diaminobenzimidazoles (cf. Section IV.D.1).

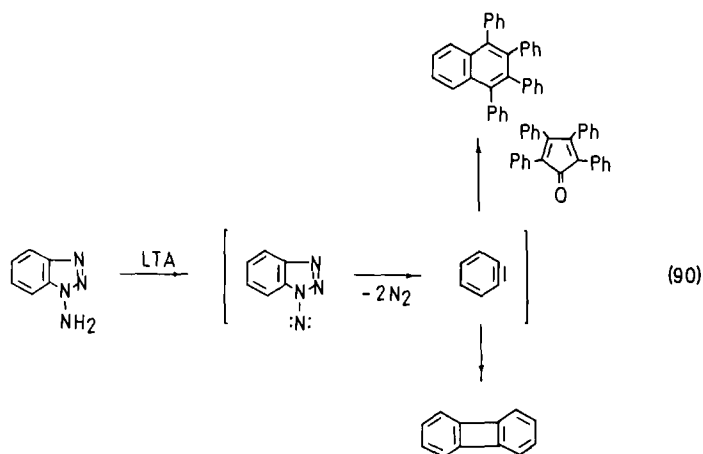


5. *N*-Amino-1,2,3-triazoles

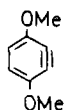
1-Amino-1,2,3-triazoles, on oxidation with LTA (88M1041) or 1-chlorobenzotriazole [69JCS(C)1474], undergo fragmentation by elimination of two equivalents of nitrogen and by formation of the corresponding acetylene [Eq. (81)]. The C₆—C₈ cycloalkynes were generated by this method (61CB3260; 64AG144). 2-Amino-1,2,3-triazoles are oxidized to give the nitrile by elimination of one equivalent of nitrogen [Eq. (89)] (88M1041).



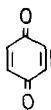
Of important synthetic significance is the oxidation of condensed *N*-amino-1,2,3-triazoles, first investigated by Rees and co-workers [65CC192; 69JCS(C)742, 69JCS(C)752, 69JCS(C)1474]. They showed that oxidation of 1-aminobenzotriazole with LTA and other oxidants leads to dehydrobenzene, which can be captured by various traps such as tetracyclone to yield 1,2,3,4-tetraphenylnaphthalene. In the absence of traps, diphenylene and triphenylene are formed in yields of 83% and 0.5%, respectively [Eq. (90)]. No other method of benzyne generation produces such a large amount of diphenylene.



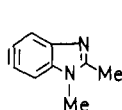
By this method, 1,2- and 2,3-dehydronaphthalenes [67JCS(C)1276; 69JCS(C)765], 9,10-phenanthryne [72JCS(P1)634], arynes, and hetarynes **336**, **337** [70JCS(C)583], **338** (70CC1458), and **339** [75JCS(P1)1747] were generated from 1-amino derivatives of the corresponding 1,2,3-triazoles.



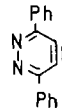
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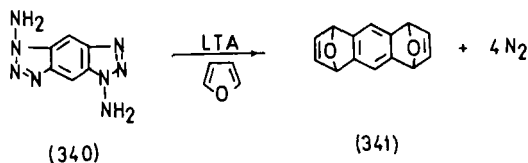


(338)

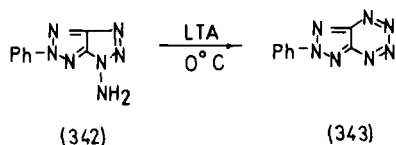


(339)

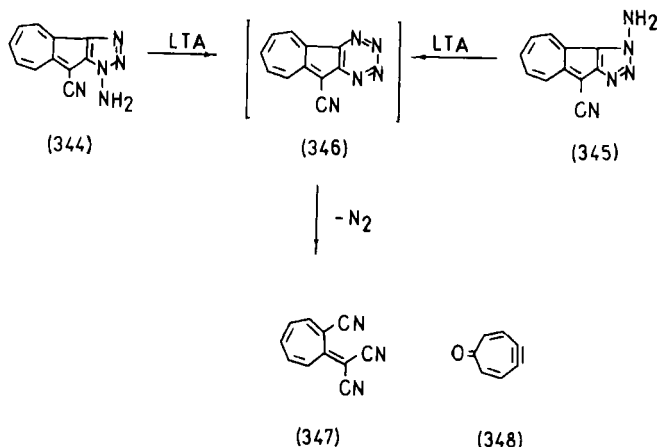
Diamine **340** was used as a synthetic equivalent of the hypothetical 1,4-benzodiyne (86JOC979). Its oxidation in the presence of furan gave rise to diendoxide **341** with 79% yield, isolated as a mixture of *syn*- and *anti*-isomers.



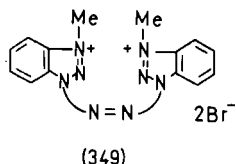
Japanese chemists, on oxidation of 1-amino-5-phenyl-1,2,3-triazolo[4,5-*d*]-1,2,3-triazole (**342**), obtained tetrazine **343** with 81% yield (88CC1608). This is not only the first representative of 1,2,3,4-tetrazines, but also the first example of the ring enlargement on oxidation of *N*-aminotriazoles. Probably, the reason for this involves the known instability of five-membered hetarynes, which lower the activation energy for the *N*-nitrene rearrangement relative to that for the fragmentation.



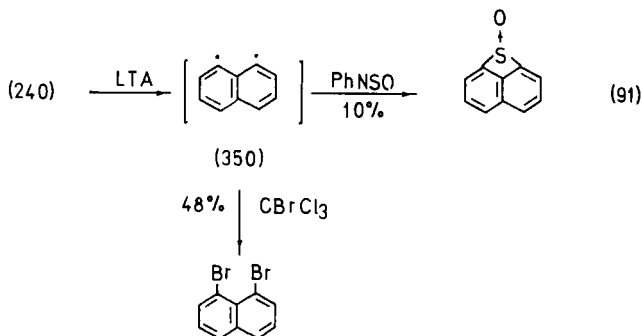
The difficulty with the formation of a five-membered aryne is, most probably, the reason for the anomalous course of oxidation of *N*-aminotriazoles **344** and **345**, leading to cycloheptatriene derivative **347**. Supposedly, the precursor of the latter compound is the unstable tetrazine **346** (85TL335). On the other hand, amine **148**, on oxidation, gives 4,5-dehydrotropone **348**, which can be captured (75AG742).



There is a single example of the oxidation of an *N*-amino-1,2,3-triazoles to a tetrazene. Under the action of bromine water on 1-amino-3-methyl-benzotriazolium salt, bisquaternary salt **349** was obtained in 59% yield [74JCS(P1)1792].



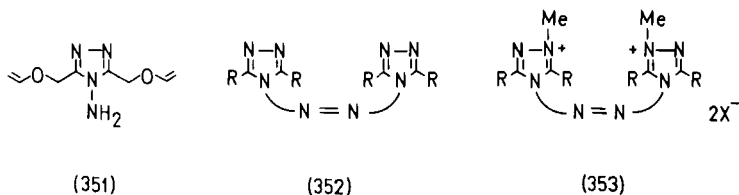
Many papers are devoted to the generation of 1,8-dehydronaphthalene (**350**) from 1-aminonaphtho[1,8-*d,e*]triazine (**240**). It was shown that **350** has a singlet biradical structure and does not give a dimer [65CC193; 69JCS(C)760]. To capture this compound, benzene [69JCS(C)760], acetylenes [69JCS(C)769], dienes (75JA681), carbon disulfide [81JCS(P1)413], diphenyl disulfide (83TL821), and *N*-sulfinylaniline [83CI(L)679] were used. Equation (91) presents some synthetic opportunities.



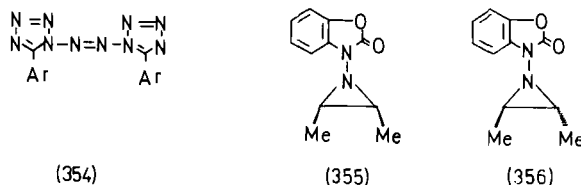
6. Other *N*-Aminoazoles

There are few data on the oxidation of other *N*-aminoazoles. 4-Amino-1,2,4-triazoles, on oxidation with lead tetraacetate, give fragmentation products in high yield, namely, nitrogen and the corresponding cyanides (70TL3851; 72TL2899; 74TL2945; 88M1041). From 4-amino-3,5-diphenyl-1,2,4-triazole [Eq. (82)] and 4-amino-1-*R*-3-phenyltriazoline-5-ones (80JHC1691), the *N*-nitrenes can be captured by alkenes. Unsubstituted 4-amino-1,2,4-triazole and its 3,5-dimethyl derivative give hotter nitrenes, which fragment completely even in the presence of traps. An attempted

intramolecular capture of an *N*-nitrene, on oxidation of *N*-amines of type **351**, also failed. At the same time, on oxidation of 3,5-dimethyl- and 3,5-diphenyl-4-amino-1,2,4-triazoles with potassium bromate in acidic medium, Glover and Rowbottom obtained 4,4'-azotriazoles **352** in moderate yield. On oxidation of 1-methyl-4-aminotriazolium salts with bromine water, biscations of 4,4'-azotriazolium (**353**) have been synthesized [74JCS(P1)1792].



Under the action of chlorine on 1-amino-5-aryltetrazoles in alkaline medium, Stolle obtained compounds he described as 1,1'-azotetrazoles **354** (33JPR1). These results need reinvestigation. If confirmed, compounds **354** will be the first known tetrazole tetrazenes.



3-Aminobenzoxazolinone (**256**), on oxidation with LTA, gives a nitrene that is easily captured by alkenes with a stereospecific addition. For instance, *cis*- and *trans*-2-butenes gave stereoisomers **355** and **356**, respectively (60–70%) [69JCS(C)772; 70JCS(C)576] (see also 69JCS(C)778).

E. *N*-AMINOAZOLES IN CYCLIZATION REACTIONS

N-Aminoazoles are a very convenient source of various heterocyclic systems having a nitrogen bridge atom. This is because both the *N*-amino group, on one hand, and the ring carbon or nitrogen atom as well as side functional groups, on the other hand, take part in cyclocondensation reactions. As a rule, they begin with the *N*-amino group, and the intermediate product (for instance, the Schiff base) can be often isolated. Only in a

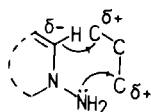
relatively few cases, at the final stage of a new ring closure, does the attack of the *N*-amino group by the side function occur.

N-Aminoazoles can react as dipolarophiles in cycloaddition reactions that lead to the annelation of new hetero-rings. These conversions are discussed at the end of Section IV,E.

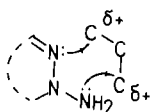
1. Cyclizations from *N*-Amino Group on Ring Atom

In terms of the electronic requirements of the reagents, these reactions can be divided into two general types. One is presented by structures **357**–**359**, and the other is presented by structure **360**. In the reactions of the first type, the ring carbon atom (as in **357**) or the aza group (as in **358**) possesses an effective negative charge; the other component necessary for cycloaddition is a bifunctional electrophile. *N*-Aminoazoles having a pronounced electron-difficient character (for instance, *N*-aminobenzimidazoles) often take part in such conversions. It is supposed that in such cases, preliminary deprotonation of a C—H bond occurs with participation of the carbanion **359** (or ylid).

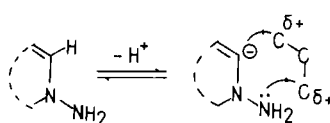
As bifunctional electrophiles, 1,3-dicarbonyl compounds are often used. In these cases, *N*-aminoazoles are built up by the pyridazine (as in **357**) or by the 1,2,3-triazine (as in **358**) cycle. The use of other bifunctional electrophiles allows the types of annelated rings to vary. The bifunctional electrophile can be replaced by two monofunctional ones, for instance, by aldehyde and nitrile, which are sequentially introduced into the reaction.



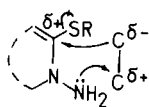
(357)



(358)



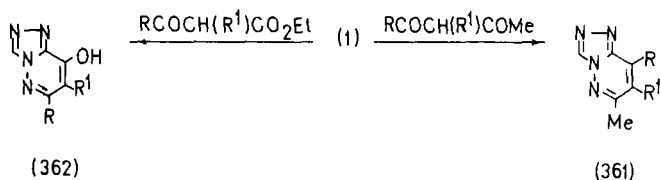
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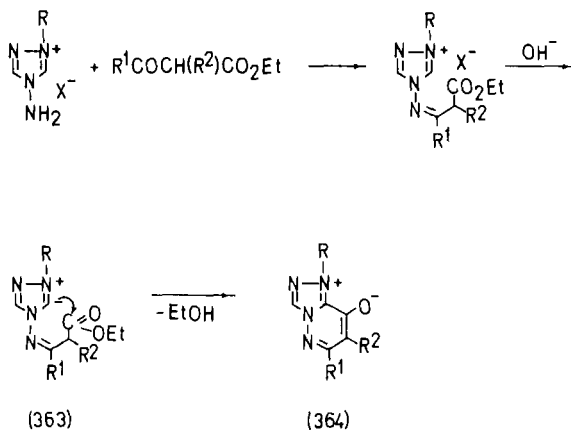
(360)

The second general type of cyclocondensation reactions is the interaction of *N*-aminoazoles with bifunctional electrophilic–nucleophilic synthons. Evidently, the ring carbon atom in such heterocyclic substrates must carry an effective positive charge. Since loss of a hydride ion is unfavorable, thio- or alkylthio derivatives of *N*-aminoazoles **360** are usually used.

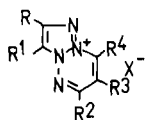
a. *With Bifunctional Electrophiles.* The first cyclocondensation reaction of an *N*-aminoazole was the interaction of 4-amino-1,2,4-triazole with acetyl- or benzoylacetone, yielding triazolo[4,3-*b*]pyridazine derivatives **361** (09CB2209). With acetoacetic ester or its derivatives, amine **1** gives only 8-hydroxy derivative **362** (09CB2594). Kost and Gentz argued in favor of the 6-hydroxy structure (58ZOB2773); however, **362** has been supported by independent syntheses (62ACS2389, 62BSF355). Many other compounds of type **362** have been obtained (59JA6289; 61FRP1248409; 68T2687; 70JPR780).



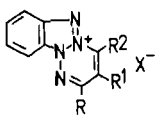
4-Amino-1-alkyl-*s*-triazolium salts, on condensation with acetoacetic ester and its derivatives, give mesoionic triazolopyridazines **364** (73JPR97). The reaction needs a base for the generation of ylid **363**.



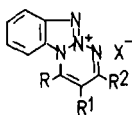
Condensation of 1-amino-1,2,3-triazoles and 1- and 2-aminobenzotriazoles with 1,3-diketones in acidic medium proceeds with participation of the ring nitrogen atom and gives triazinium salts **365**–**367** (81UKZ76). It was reported that 1-amino-1,2,3-triazole, on heating with acetoacetic ester, gives pyridazine **368**; however, these data probably need reinvestigation (52MI2).



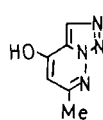
(365)



(366)

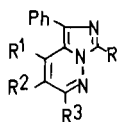


(367)

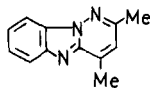


(368)

The interaction of proton salts of 1-amino-2-R-4-phenylimidazoles with β -dicarbonyl compounds occurs at position 5, yielding imidazo[1,5-*b*]pyridazines **369**, even when an amino or mercapto group is at position 2 of the imidazole ring (74KGS846; 79LA639; 88UKZ612). 1-Aminobenzimidazole condenses with acetylacetone in the presence of anhydrous zinc chloride to afford 2,4-dimethylpyridazino[1,6-*a*]benzimidazole (**370**) (83KGS386).

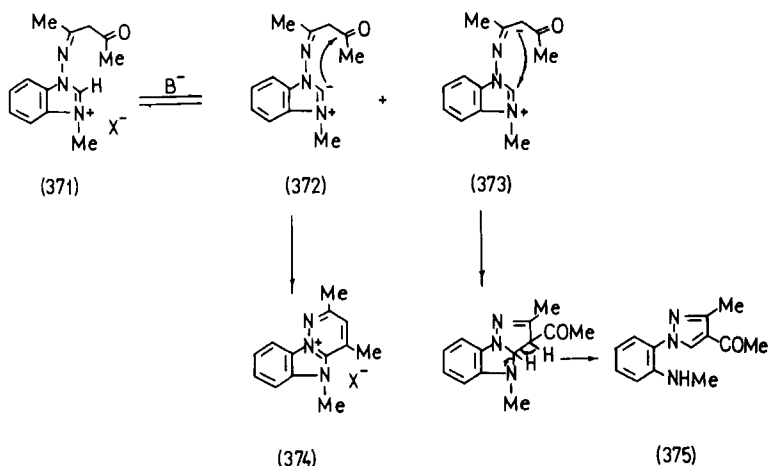


(369)

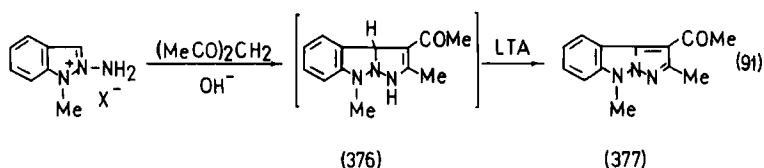


(370)

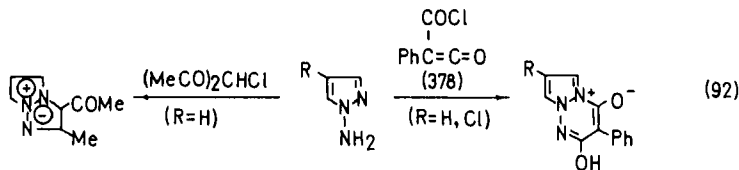
The reaction of 1-amino-3-methylbenzimidazolium salts with β -dicarbonyl compounds is interesting (83KGS256). Thus, 1-amino-3-methylbenzimidazolium iodide reacts with acetylacetone in aqueous potassium carbonate to yield, via the Schiff bases **371**, approximately equal amounts of pyridazino[1,6-*a*]benzimidazolium salt (**374**) and pyrazole derivative (**375**). If a methyl group is in position 2 of the initial salt, the only product is the pyrazole corresponding to **375**. In DMF/ K_2CO_3 , 1-amino-3-methylbenzimidazolium iodide with acetylacetone gives only salts **374**. Formation of compounds **374** and **375** can be explained as a result of competition between ylid **372**, which gives on cyclization a pyridazinium salt, and betaine **373**, which converts to a pyrazole. Obviously, the presence of a substituent at position 2 of the imidazole ring makes the former course of reaction impossible.



2-Amino-1-methylindazolium salt reacts with acetylacetone differently in comparison with *N*-aminobenzimidazolium salts [Eq. (91)] (76CPB2 267). This is explained partly by the decreased CH-acidity of the pyrazole ring and partly because the product of the primary cyclization (**376**) is not stabilized by ring opening, but is aromatized by the oxidant to pyrazolo[1,5-*b*]indazole (**377**).

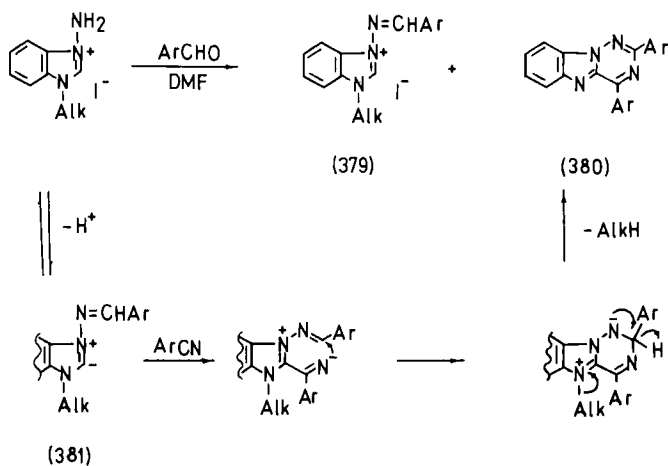


Chloroacetylacetone and ketene **378** are other bifunctional electrophiles investigated in cyclizations with 1-aminopyrazoles [Eq. (92)] (78TL1291; 83H1271).

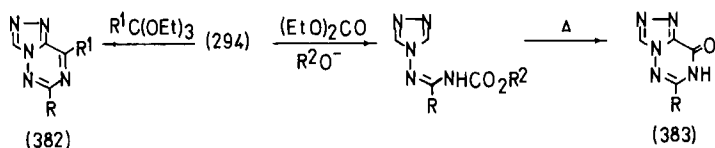


More complicated examples of cyclocondensation are reactions where *N*-aminoazole reacts sequentially with two monofunctional electrophiles,

although the process looks like the action of one bifunctional electrophile. Thus, 1-amino-3-alkylbenzimidazolium salts, on heating with aromatic aldehydes in DMF, along with the expected Schiff bases (379) gives 1,2,4-triazino[1,6-*a*]benzimidazole derivatives (380) (86KGS346). Obviously, some of salt 379 eliminates a molecule of aryl cyanide, which reacts further with ylid 381 formed *in situ*.



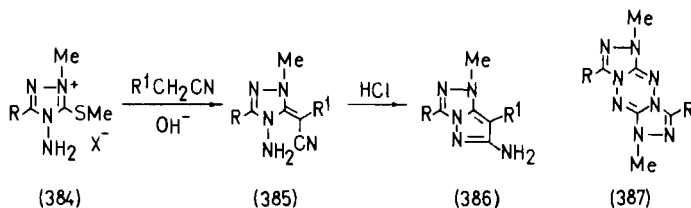
Becker and co-workers synthesized 1,2,4-triazolo[3,4-*f*]-1,2,4-triazines **382** and **383** by cyclization of amidines **294** with ortho-esters or diethyl carbonate (69JPR646; 70JPR669).



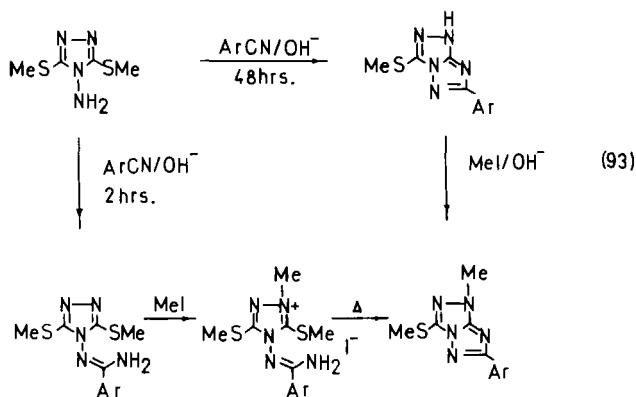
b. With Bifunctional Amphoteric Synthons. As already mentioned, such heterocyclizations require a good leaving group, usually the alkylthio group, at the α -carbon ring atom. Characteristic examples are the interaction of 4-aminotriazolium salts **384** with malonic ester and other active methylene compounds in the presence of bases (85H641). These reactions first lead to the methylene bases **385**, which are cyclized to pyrazolo[1,5-*c*]-1,2,4-triazoles (**386**) by mineral acids. If the initial methylene compounds do not possess a high CH-acidity (for instance, if R' = CONH₂ or CONHNH₂), the yield of **386** falls to 20–30%, and tricyclic tetrazines **387**

are additional products of the reaction as a result of interaction of two molecules of the salt **384** (73JPR1131; 85H641).

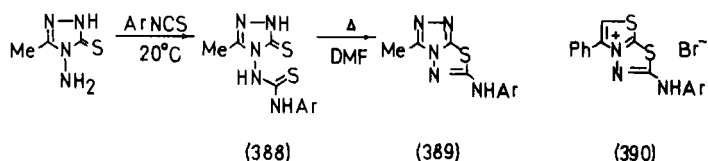
Similar behavior towards methylene-active compounds is found for 3-amino-3-alkylthiothiazolium (87H1323) and 1-amino-2-alkylthiobenzimidazolium salts (90KGS1689).



As shown in Eq. (93), aryl cyanides can also play a role as bifunctional synthons in similar conversions that lead to annelation of the 1,2,4-triazole ring (83S415; 85BCJ735, 85H2613).

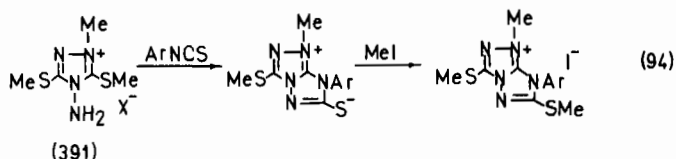


Reaction of thio- and alkylthio derivatives of *N*-aminoazoles with aryl isothiocyanates leads to annelation of a 1,3,4-thiadiazole or a 1,2,4-triazole ring. Thus, 4-amino-3-methyl-1,2,4-triazoline-5-thione, on reaction with aryl isothiocyanates under mild conditions, gives products of addition (**388**), which on heating are transformed to 2-arylaminotriazolo[3,4-*b*]thiadiazoles (**389**) (83S411; 87JHC1173).

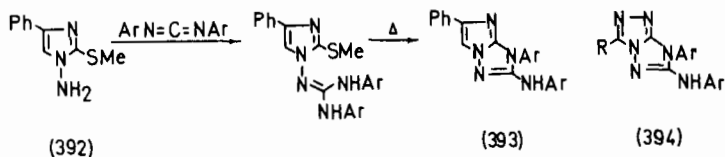


A similar reaction that yielded salt **390** was described for 3-amino-2-benzylthio-4-phenylthiazolium bromide (88S729). However, in the case of 4-aminotriazolium salt **391**, the course of cyclocondensation was different [Eq. (94)] (84TL5427; 86T2121).

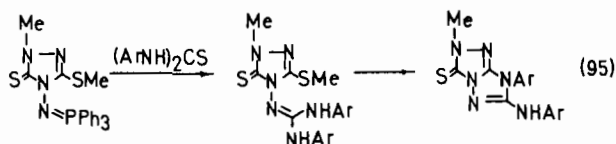
1-Amino-2-methylthio-4-phenylimidazole reacts with alkyl- and arylisothiocyanates, giving rise to derivatives of imidazo[1,2-*b*][1,2,4]thiazole (89S843).



The use of diarylcarbodiimides as bifunctional amphoteric synthons also leads to annelation of the 1,2,4-triazoles ring. A typical example is the conversion of *N*-aminoimidazole **392** to imidazo[1,2-*b*]triazoles **393** (88H161). Similarly, triazolo[4,3-*b*]triazoles **394** have been synthesized from 4-amino-*s*-triazoline-5-thiones [68JCS(C)2099; 88H161].



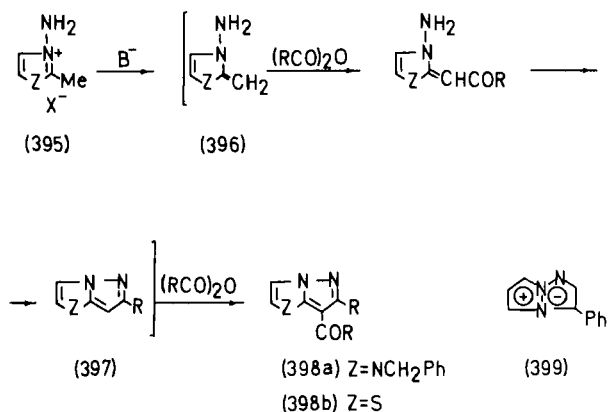
Instead of diarylcarbodiimides, one can also use diarylthioureas in such conversions. However, in this case, preliminary activation of the *N*-amino group is necessary, for instance, by its transformation to the phosphazo group [Eq. (95)] [88JCS(P1)2667].



2. Cyclization of an *N*-Amino Group onto a Methyl Substituent

N-Aminoimidazolium and *N*-aminothiazolium salts (**395**) containing a methyl group at position 2, on heating with anhydrides in the presence of a

base, are cyclized to yield acyl-substituted imidazo[1,2-*b*]pyrazoles (**398a**) and pyrazolo[5,1-*b*]thiazoles (**398b**) (74CPB482). 1-Amino-2-methyl-3-*R*-benzimidazolium (74CPB482; 80KGS814) and 1-amino-2,3-dimethylperimidinium (80KGS93) salts also take part in analogous conversions. In these reactions, methylene anhydrobases **396** may be formed as intermediates, which further undergo acylation and cyclization. The appearance of an acyl group in the final product is probably connected with acylation of the first formed pyrazoloazole **397**, a conclusion supported by special experiments on acylation of **397**. One can imagine formation of **398** as the result of cyclization of diacyl-substituted methylene anhydrobase, a less likely prospect.

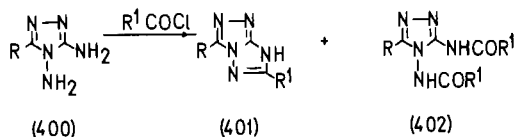


1-Amino-2-phenacylpyrazolium mesitylsulfonate, obtained on amination of 1-phenylpyrazole with MSH, is cyclized to mesoionic bicyclic compound **399** on treatment with KCO_3 (78TL1291).

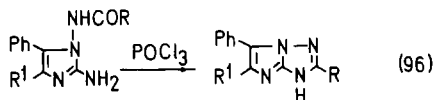
3. Cyclizations of *N*-Amino Groups onto Amino and Hydrazino Substituents

Most information on cyclocondensation reactions of *N*-aminoazoles is concerned with vicinal *N,C*-diaminoazoles. In most cases, reactions were carried out with various carbonyl-containing compounds: carboxylic acids and their derivatives, aldehydes and ketones, 1,2- and 1,3-dicarbonyl compounds, etc. Depending on the structure of these synthons, cyclocondensations lead to the formation of five-, and six- or seven-membered heterocycles.

a. *With Carboxylic Acids and their Derivatives.* 3,4-Diaminotriazoles **400**, on heating with anhydrides or acid chlorides, are converted to 1,2,4-triazolo[4,3-*b*]triazole derivatives (**401**) (50JCS614; 62LA148). As side products, diacetyl derivatives of the initial diamine **402** are sometimes formed.

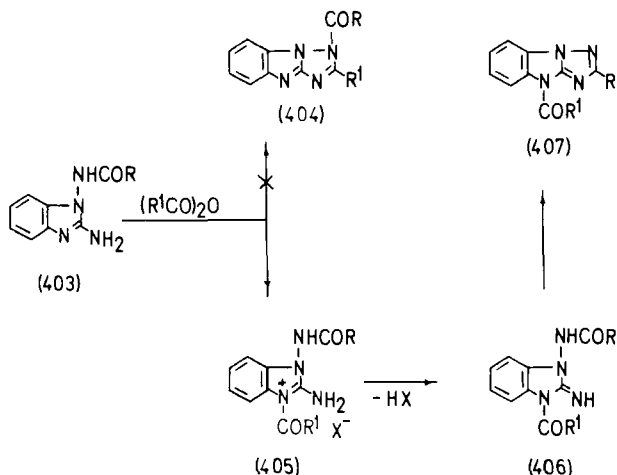


The most obvious channel to cyclization is acylation of the *N*-amino group (cf. Section IV,C,2), followed by using closure in the case of *N*-monoacylamino derivatives. The latter compounds are often isolated and then cyclized on heating with various dehydrating substances (PPA, POCl₃, etc.). A characteristic example is shown in Eq. (96) (70CB2845, 70CB3533).

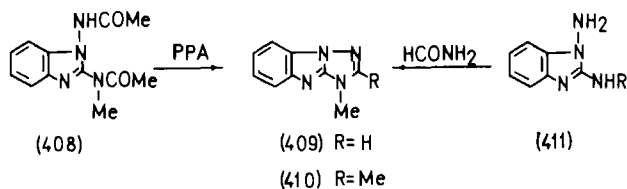


At the same time, it was not possible to cyclize 7-acylamino-8-aminotheophylline, even on long-term heating with anhydrides acid or in PPA (87KGS1398). The cyclization of 1-acylamino-2-aminobenzimidazoles (**403**) proceeds not by a simple course. Ho and Day described products, formed on refluxing **403** in acetic or benzoic anhydride, as 1-acyl-2-*R*-triazolo[1,5-*a*]benzimidazoles (**404**) (73JOC3084). However, reinvestigation showed that, in fact, the compounds are 4-acyl derivatives (**407**) (89KGS209). Probably, cyclization proceeds via salt **405** and then via imine **406**.

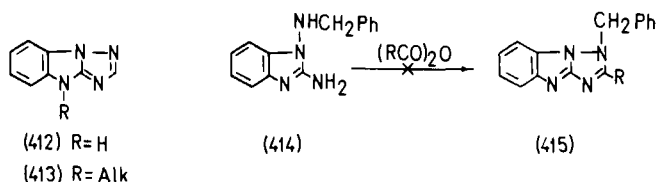
Theoretically, compounds **404** could be formed on cyclization of 1,2-bis(acylamino)benzimidazole. However, such diacyldiamines, as a rule, are not cyclized (73JHC947). The only example is the synthesis of 2,3-dimethyltriazolo[1,5-*a*]benzimidazole (**410**), on heating compound **408** in PPA (88KGS1070). Although 1,2-diaminobenzimidazole is easily cyclized into 2-*R*-triazolo[1,5-*a*]benzimidazoles, on refluxing with anhydrides (*R* = Me, Ph) (73JOC3084; 89KGS209), by contrast, 1-amino-2-alkylaminobenzimidazoles **411** are not cyclized under the same conditions



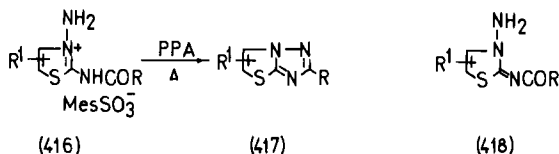
(88KGS1070; 89KGS209). Only on refluxing 1-amino-2-methylaminobenzimidazole (**411**, R = Me) in formamide or in a mixture of HC(OEt)₃/Ac₂O was it possible to obtain **409** in moderate yield.



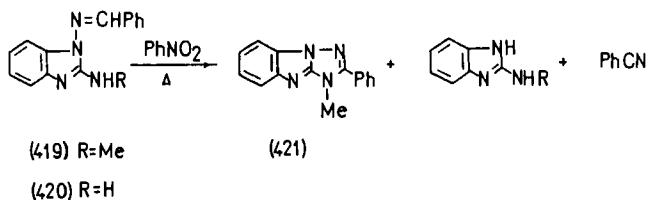
Using formamide is especially good for obtaining unsubstituted triazolo[1,5-a]benzimidazole (**412**) and its 4-R derivatives (**413**) from 1,2-diaminobenzimidazole and 1,2-diamino-3-R-benzimidazolium salts, respectively (89KGS209). It was not possible to synthesize 1-substituted triazolo[1,5-a]benzimidazoles, for instance, **415** from 1-benzylamino-2-aminobenzimidazole (**414**). The only products of the reaction were diacyl derivatives of the initial diamine (89KGS209).



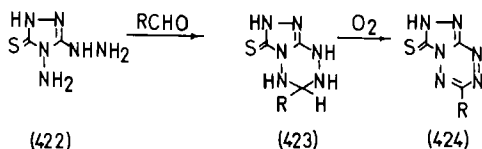
Cyclization reactions leading to the corresponding condensed 1,2,4-triazoles have also been carried out for 2,3-diaminothiazolium, benzothiazolium (73JHC947; 74JHC459), naphtho[1,2-*d*]thiazolium (84JHC1571; 87JHC1729), and 1,3,4-thiadiazolium salts (79CPB2521). It was shown (73JHC947) that, for instance, the cyclization of 1,2,4-triazole proceeds especially readily if the initial compounds are 2-acylaminothiazolium salts (**416**) heated above melting points, or better yet, in PPA. Interestingly, unlike **416**, neutral acylamine **418** are not cyclized on thermolysis because of the less reacting carbonyl carbon atom.



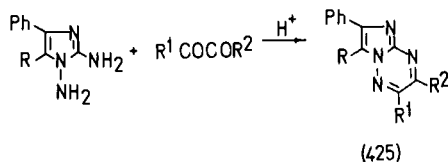
b. *Oxidative Cyclization of Schiff Bases.* On heating in nitrobenzene, 1-arylideneamino-2-methylaminobenzimidazoles (**419**) undergo oxidative cyclization, affording **421** in yields of 20–30% (88KGS1226). Low yields are explained by elimination of the 1-substituent with formation of 2-methylaminobenzimidazole and arylcyanide. Under the same conditions, 1-benzylideneamino-2-aminobenzimidazole (**420**) quantitatively loses benzonitrile to yield 2-aminobenzimidazole. Attempted cyclization of **420**, under the action of cupric acetate (77JOC542), and of 7-benzylideneamino-8-aminotheophylline with MnO_2 and nitrobenzene (87KGS1398) failed.



4-Amino-3-hydrazino-1,2,4-triazoline-5-thione (**422**) under the action of aldehydes readily gives unstable products **423**, which readily air oxidize to the deeply colored tetrazines **424**. This reaction was suggested as a sensitive method for determining aldehydes (70CC1719).

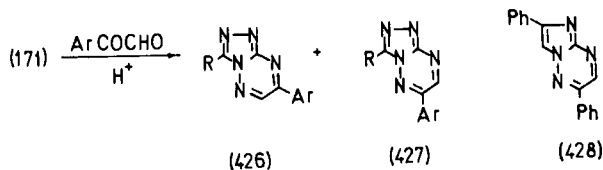


c. *With 1,2-Dicarbonyl Compounds.* Vicinal *N,C*-diaminoazoles easily take part in acid-catalyzed condensation with 1,2-dicarbonyl compounds: glyoxal, ketoaldehydes, diketones, ketocarboxylic acids, *ortho*-quinones, isatin, etc. Occasionally, monooximes of ketoaldehydes and *N*-acylamino-*C*-aminoazoles are used in these reactions. Condensations, as a rule, proceed in good yield and lead to annelation of the 1,2,4-triazine ring. A typical example is the synthesis of imidazo[2,1-*b*]-1,2,4-triazines (**425**) from 1,2-diaminoimidazoles (70CB3533; 73KGS1190; 74JHC327; 82KGS236, 82KGS242).



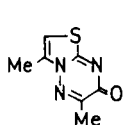
Analogous reactions were carried out with 1,5-diaminoimidazoles (74BSF1453), 1,2-diaminobenzimidazoles (73JOC3084; 77JOC542; 79H1001; 84ZOR1345; 85KGS1402; 87KGS533; 88KGS1070), 7,8-diaminotheophylline (87CPB4031, 87KGS1398; 88JHC791), 1,5-diaminopyrazoles (86S71), 1,5-diaminotetrazoles (88JOC5371), 2,3-diaminotriazolium salts (67ACH385), and 3,4-diamino-1,2,4-triazoles (50JCS614, 50JCS1579; 52JCS4817; 54JA619; 64BEP642615; 64CB2179; 67ACH385; 69BSF2492; 73UKZ1040; 77JOC1018; 79JHC1393; 80UKZ1092).

If $\text{R}^1 \neq \text{R}^2$ in the initial α -dicarbonyl compound, the formation of two isomeric triazines is possible. Thus, 3,4-diamino-*s*-triazoles **171** react with arylglyoxals, yielding a mixture of **426** and **427**, where the 7-aryl-substituted derivatives **427** prevail (79JHC1393). The latter are the only products in the case of phenylglyoxal oxime. Thus, the aldehyde group of aryl glyoxals reacts predominantly with the *N*-amino group of 3,4-diaminotriazole. However, the product of interaction of 1-acetylamino-2-amino-4-phenylimidazole with phenyl glyoxal was described as **428** on the basis of IR spectral data (70CB3533).

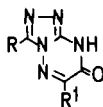


Products of the interaction of *N,C*-diaminoazoles with α -ketocarboxylic acids were described by most investigators to be structures of type

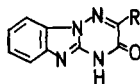
429 (67ACH385), **430** (64FRP1379480; 67ACH385; 69BSF2492), or **431** (73JOC3084; 85KGS1402; 87KGS533; 88KGS1070). In this connection, structure **432** describing products of interaction of α -ketocarboxylic acids with 1,2-diaminoimidazoles (74JHC327) is doubtful.



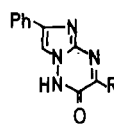
(429)



(430)

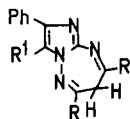


(431)

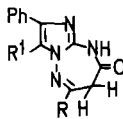


(432)

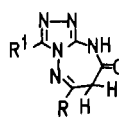
d. *With 1,3-Dicarbonyl Compounds and α,β -Unsaturated Ketones.* In an acidic medium, acetylacetone and other 1,3-diketones are condensed with *N,C*-diaminoazoles to yield 1,2,4-triazepines, as does compound **433** in the case of 1,2-diaminoimidazoles (83ZOR433). Analogous compounds were also obtained from 1,5-diaminoimidazoles (74BSF1453), 1,2-diaminobenzimidazoles (88T7185), 1,5-diaminotetrazole (84KGS1683), and 7,8-diaminotheophiline (88JHC791). In the latter case, one can isolate the intermediate Schiff base, which is cyclized to the corresponding triazepine on heating with PPA.



(433)



(434)

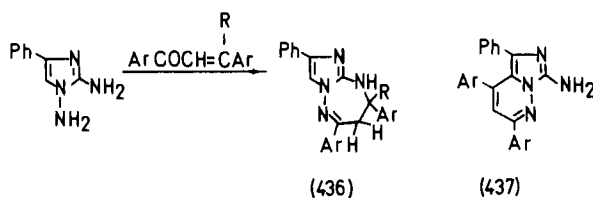


(435)

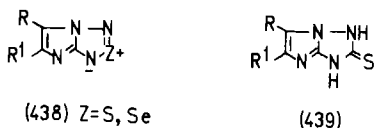
1,2-Diaminoimidazoles react with aceto- and benzoylacetic esters to afford triazepinone **434** (79LA639). Analogous products (**435**) are obtained under the same conditions from 3,4-diamino-*s*-triazoles (70AP709; 74JHC751; 75CSC317, 75JHC661; 85M11), although they were first described by a mistaken structure with the oxo group at position 6 (70AP709). 1,5-Diaminoimidazoles (78JHC937) and 1,2-diaminobenzimidazoles (84KGS700; 88T7185) react with acetoacetic ester and its derivatives with complications.

1,2-Diamino-4-phenylimidazole reacts with aromatic α,β -unsaturated ketones in an acidic medium to yield triazepines **436** (83KGS93). If the reaction is carried out in alkaline medium with benzylidene acetophenone,

imidazo[1,5-*b*]pyridazine derivative (**437**) is also formed in small amounts (88UKZ612). Interestingly, the formation of **436** also occurs on heating 1,2-diamino-4-phenylimidazole with aryl methyl ketones (84KGS1396). Probably, the latter compounds in this case undergo self-condensation to α,β -unsaturated ketones, and those react further with diamine. The reaction of 1,2-diaminobenzimidazole with α,β -unsaturated ketone is discussed in Section IV,E,5.

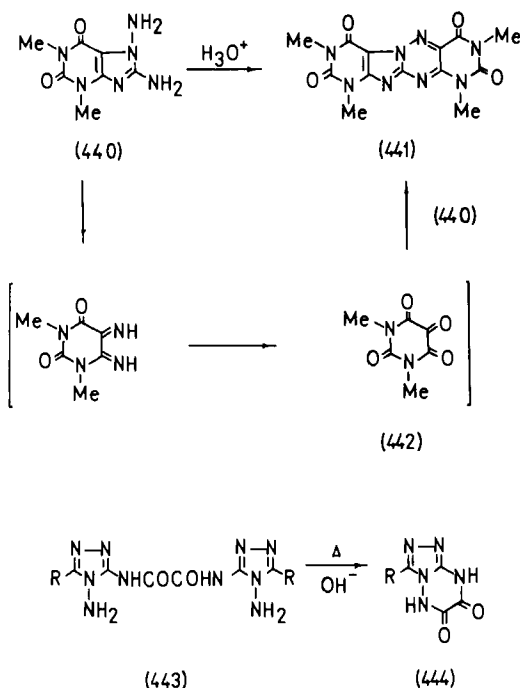


e. *Other Types of Cyclizations.* 1,2-Diamino derivatives of imidazole and benzimidazole interact with thionyl chloride in pyridine or with selenium dioxide in ethanol to yield unstable heteropentalenes **438** (81JOC4065). Carbon disulfide converts these diamines in alkali into imidazo[1,2-*b*]triazoline-2-thiones (**439**) (70CB3533).

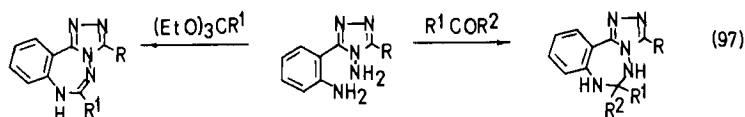


7,8-Diaminotheophyllines (**440**) undergoes an unexpected transformation on heating with acids. Tetracyclic compound **441** is formed in 74% yield (87CPB4031, 87KGS1398) (in the latter paper this compound was described as an isomeric structure with unsymmetrical location of the C=O groups). Perhaps under the reaction conditions, diamine **440** is partially decomposed to afford dimethylalloxane **442**, then reacts with the latter compound to yield **441**. This proposal was supported by the synthesis of **441** from alloxane and diamine **440** (87CPB4031). However, an alternative mechanism of formation of **441** was described (87KGS1398).

On heating in alkaline solution, the bisoxalyl derivative of 3,4-diamino-5-triazole (**443**) is cyclized to triazolo[3,4-*b*]-1,2,4-triazine-6,7-dione (**444**) (70AP650).



Equation (97) illustrates examples of cyclizations with participation of the *N*-amino group and a more remote amino group in a side chain [72JCS(P1)1842].

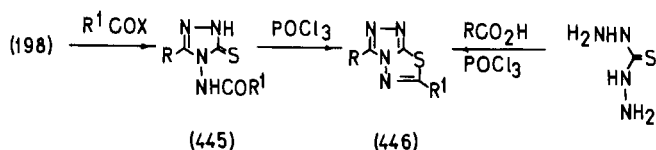


4. Cyclizations of *N*-Amino Groups onto Mercapto and Hydroxy Groups

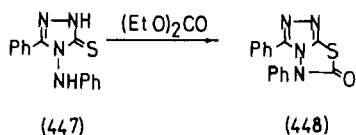
Almost all such cyclizations were carried out with α -thio derivatives of 4-amino-*s*-triazole and 1-aminoimidazole. As cyclizing agents, two groups of compounds were mainly used: (1) carboxylic acids and their derivatives, and (2) α -halogenocarbonyl compounds. In the former case, annelation

takes place to give a 1,3,4-thiadiazole ring; in the latter case, a 1,3,4-thiadiazine ring is constructed by annelation.

The interaction of 4-amino-1,2,4-triazoline-3-thiones (**198**) with carboxylic acids (73JHC387; 82JIC769; 87JHC1173) or with their acid chlorides (56YZ1133; 57CPB385; 87JPS395) in the presence of phosphorus oxychloride leads to 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives (**446**). The intermediate products of the reaction are *N*-acylaminotriazoles **445**, which can be isolated and cyclized into **446** on heating with phosphorus oxychloride (84JHC1689). Compounds **446** can be synthesized also on heating thiocarbohydrazide with carboxylic acids in the presence of POCl_3 (73JHC387).

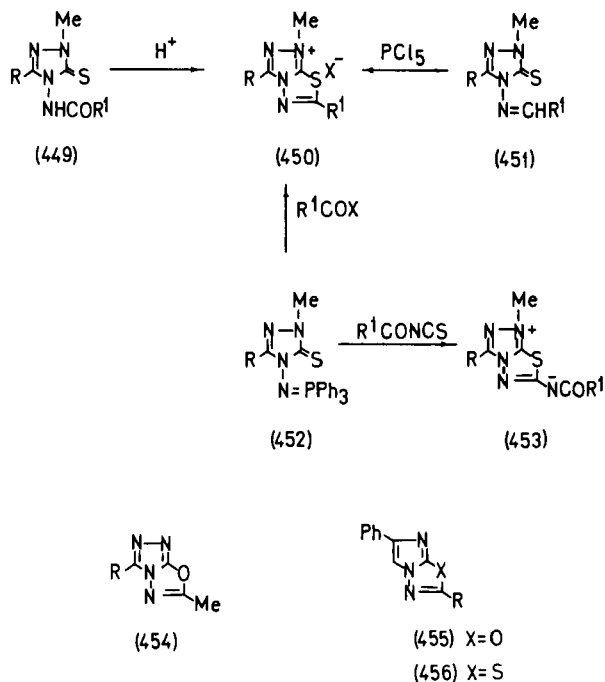


Cyclization of aminothiones **198** with carbon disulfide, bromocyanogen, aryl isothiocyanates, and 1-bromo-2-acetylacetylene leads to mercapto, amino, arylamino, and acetylmethyl derivatives of triazolo[3,4-*b*]-1,3,4-thiadiazole (**446**, $\text{R}' = \text{SH}, \text{NH}_2, \text{NHAr}, \text{CH}_2\text{COMe}$), respectively [64CI(L)1919; 66JOC3528; 81JHC1353; 86JHC1439; 87JHC1173; 87JPS395; 88ZOR2151]. The reaction of aminothione **447** with diethyl carbonate gives rise to the oxo derivative **448** (84JHC1689).

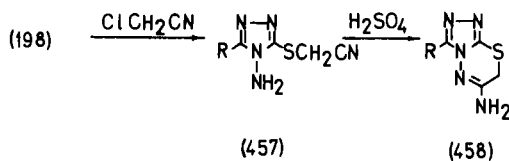


1,2,4-Triazolo[3,4-*b*]thiadiazolium salts (**450**) are prepared by three methods: (1) acidic cyclization of *N*-acylaminothiones **449**, (2) the action of PCl_5 on Schiff bases **451**, and (3) interaction of phosphazo compounds **452** with acyl halogenides. On the basis of phosphazo compounds and acyl isothiocyanates, betaines **453** have also been synthesized (86LA1540).

With the help of analogous reactions, 1,2,4-triazolo[3,4-*b*]-1,3,4-oxadiazoles (**454**) were synthesized from 4-acylamino-1,2,4-triazoline-3-one (80JHC1691), and the derivatives of imidazo[2,1-*b*]-1,3,4-oxadiazole (**455**) and imidazo[2,1-*b*]thiadiazole (**456**) were obtained from *N*-aminoimidazoline-2-ones and *N*-aminoimidzoaline-2-thiones, respectively (62ZC153; 63LA113; 69ZC337; 70CB272; 88H1935).

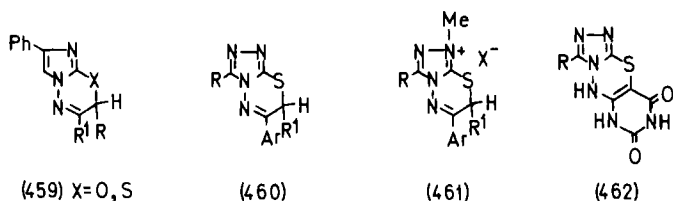


Aminothiones **198** are alkylated with chloroacetonitrile on the sulfur atom (73JPR1131; 87JHC1173). The resultant cyanomethyl derivative **457** is cyclized to 1,3,4-thiadiazine **458** on heating with concentrated sulfuric acid (87JHC1173).

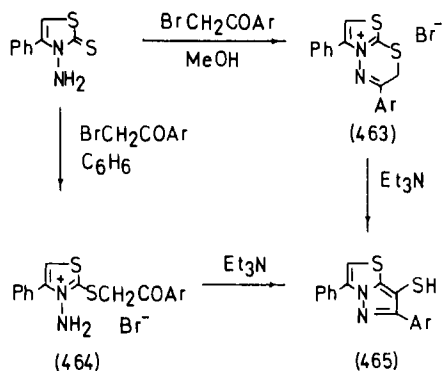


A more general method for synthesizing condensed thiadiazines is the reaction of *N*-amino- α -thioazoles with α -halogenocarbonyl compounds. An analogous approach may be applied to synthesis of 1,3,4-oxadiazines from *N*-amino- α -oxoazoles. Thus, for instance, one can obtain bicyclic compounds **459** from the corresponding *N*-aminoimidazoles (63LA113; 70CB272) and compounds **460** and **461** from 4-aminotriazoline-3-thiones [52JCS4811; 73JPR1131; 82JIC900; 83JPS45; 85CS230; 86IJC382,

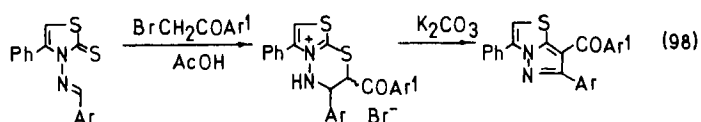
86JCR(S)70, 86JHC1439]. The interaction of aminothiones **198** with 5-bromobarbituric acid gives tricyclic compounds **462** (85M633).



Reaction of 3-amino-4-phenylthiazolin-2-thione with phenacyl bromides in methanol leads to thiadiazinium cation **463**. The latter compounds, on treatment with triethylamine, is converted to pyrazolo[5,1-*b*]thiazole derivative (**465**). The same reaction in benzene first gives the *S*-phenacyl derivative **464**, which is transformed to **465** in the presence of bases (87H1323).



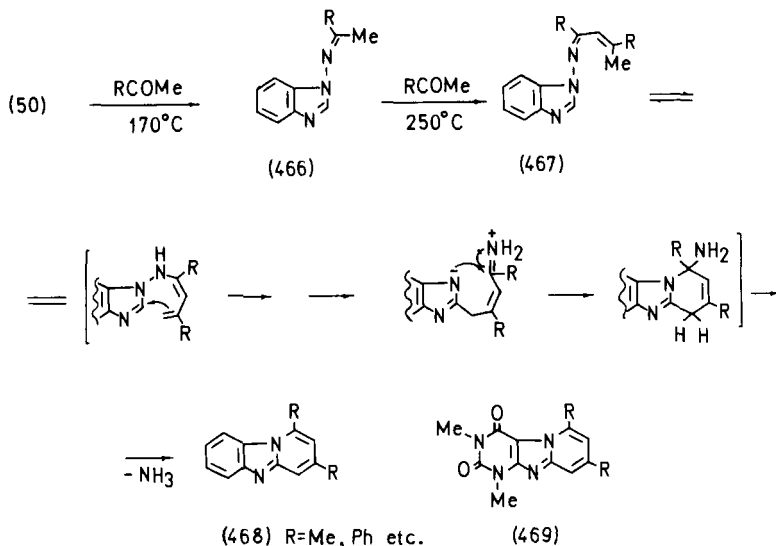
Cyclization of phenacyl halogenides with Schiff bases obtained from aminothiones of 1,2,4-triazole [87JCS(P1)1853] and thiazoles (88S729) proceeds by a somewhat different course [Eq. (98)].



5. Cyclizations with Loss of an *N*-Amino Group

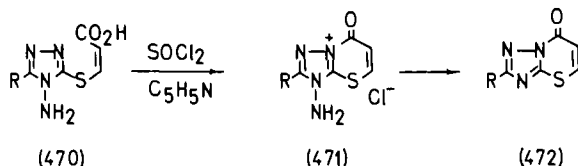
In some cases, the heterocyclizations of *N*-aminoazoles are accompanied by the loss of an *N*-amino group. For instance, on heating 1-amino-benzimidazole (50) with acetone or acetophenone in the presence of anhydrous zinc chloride at 200–250°C, pyrido[1,2-*a*]benzimidazoles (468) are formed in good yields (81KGS1497). The same reaction, with formation of compound 469, was observed for 7-aminotheophylline (87KGS1551).

It was assumed that the mechanism resembles to some extent the mechanism of the Fischer reaction. Undoubtedly, the primary products of the reactions are the Schiff bases 466 and 467. The former can be isolated if the reaction is carried out at a lower temperature. The formation of 467 is supported by the noticeably increased yield of 468 if mesityl oxide or dypnone are used in reaction instead of acetone or acetophenone. Further steps include tautomerization of Schiff base 467, the attack by the terminal methylene group on electron-deficient position 2 in the imidazole ring, the cleavage of an N—N bond, and recyclization followed by aromatization with elimination of a molecule of ammonia.

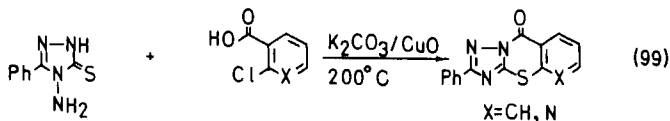


Elimination of the *N*-amino group takes place by another mechanism on formation of triazolo[3,2-*b*]thiazinones (472) as a result of the interaction of 1,2,4-triazolythioacrylic acids (470) with thionyl chloride in pyridine. In this case, the cyclization includes acylation of the cyclic aza group af-

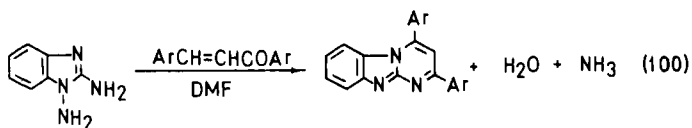
fording cation **471**, which then, probably under the action of pyridine, eliminates the amino group. The isolation of salts **471** ($R = Ph$) supports such an explanation (80JOC2479).



Another example of a similar cyclization is presented in Eq. (99) [88IJC(B)1049].



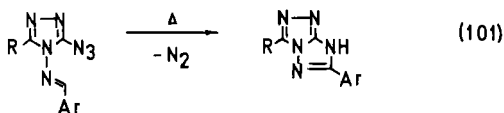
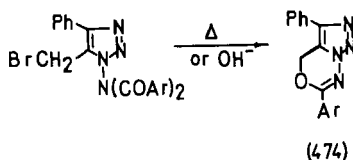
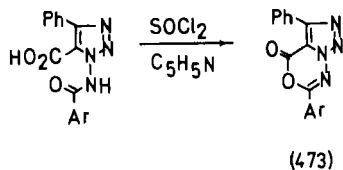
1,2-Diaminobenzimidazole reacts with chalcones on refluxing in DMF to yield pyrimido[1,2-a]benzimidazoles [Eq. (100)] (86KGS1136; 89KGS1071). The course and mechanism of this reaction are not fully clear, taking into account that the *N*-amino group must be considerably more active towards carbonyl compounds than the 2-amino group (cf. Section IV,C,3).



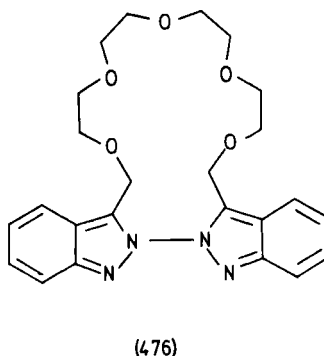
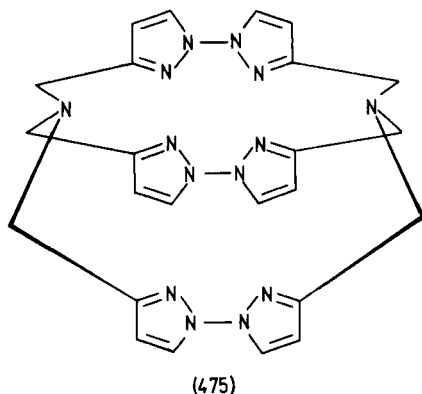
6. Miscellaneous Types of Cyclization

Triazolo[1,5-d]-1,3,4-oxadiazines **473** and **474** have been synthesized from 1-aroilamino- and 1-diaroilylamino-1,2,3-triazoles [85JCS(P1)1167; 87JHC1275].

Thermolysis of 3-azido-4-arylideneamino-1,2,4-triazoles leads to 2-aryl-triazolo[3,2-c]triazoles, supposedly as a result of the insertion of a nitrene intermediate into the azomethine bond [Eq. (101)] (65JOC711; 66JHC119).



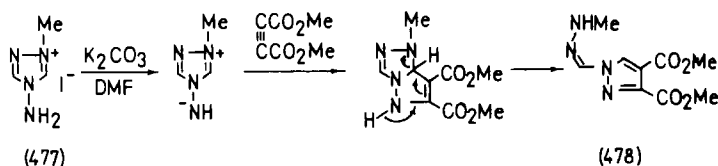
Mendoza and co-workers, on the basis of 3,3'-dibromomethyl derivatives of 1,1'-dipyrazolyl and 2,2'-diindazolyl, synthesized cryptand **475** and crown-ether **476** (85CC1765; 88JOC2055). Similar crown-ethers were also obtained with 4-amino-1,2,4-triazoles (87H989).



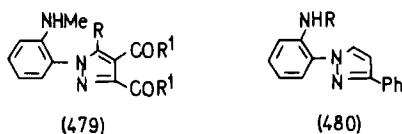
7. Cycloaddition Reactions

N-Iminoazolium betaines, like all azomethine-imides, take part in 1,3-dipolar cycloadditions with various dipolarophiles: activated acetylenes

and ethylenes, arylisothiocyanates, etc. The primary product of cycloaddition can sometimes be isolated, but usually it undergoes further conversions by a course dependent on the presence of a substituent at the *N*-amino group and on the nature of this substituent. As a rule, *N*-iminoazolium betains with an unsubstituted NH group give adducts stabilized by the opening of the hetero-ring attached to the *N*-amino group. The products of these reactions are 1-substituted pyrazoles. For instance, 4-amino-1-methyl-1,2,4-triazolium iodide (**477**) reacts with dimethyl acetylenedicarboxylate (DMAD) in the presence of K_2CO_3 to afford pyrazole **478** (76CPB2568).



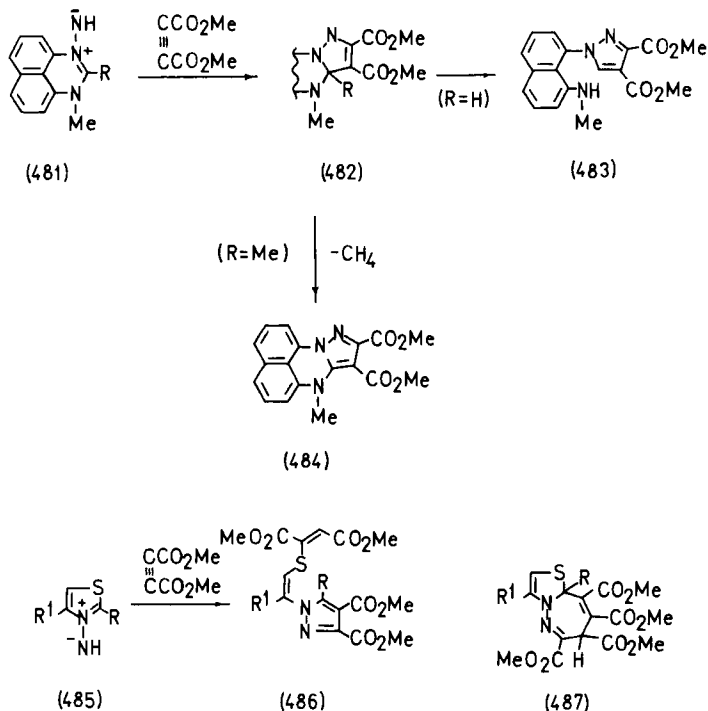
Similarly, 1-amino-3-alkylbenzimidazolium salts react with acetylenedicarboxylic esters [73CI(L)952; 75JHC225] and cuprous and silver phenylacetylenides (84ZOB1676) to yield 1-(*o*-aminophenyl)pyrazoles **479** and **480**.



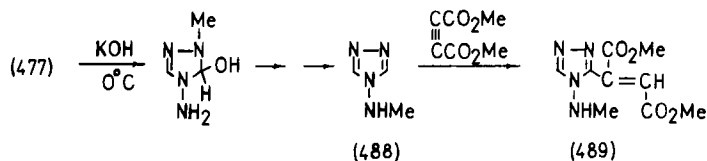
Perimidinium imides **481** form with DMAD adducts **482**, and the subsequent pathway to product for the latter compounds depends on the substituent R. If R = H, the corresponding pyrazole derivative **483** is formed as described earlier. However, if R = Me, elimination of a molecule of methane is observed, and pyrazolo[1,5-*a*]perimidine derivative **484** is formed (83CPB1378).

Thiazolium imides **485** react with DMAD, yielding adducts in a ratio of 1:2. These adducts were first described by structure **487** (74CPB482). However, it was shown later that these compounds are pyrazoles **486** (77JOC1648).

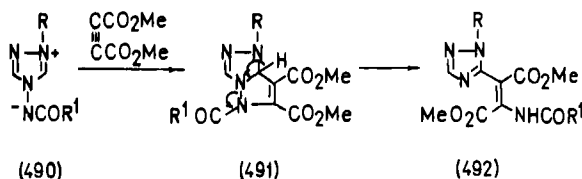
In all the papers just cited, *N*-imides of azoles were generated by the action of mild bases (K_2CO_3 , Et_3N , etc.) on *N*-aminoazolium salts. In one case, when potassium hydroxide was used as a base in DMF, an anomalous reaction course was observed. Thus, salt **477** gave, with DMAD, the



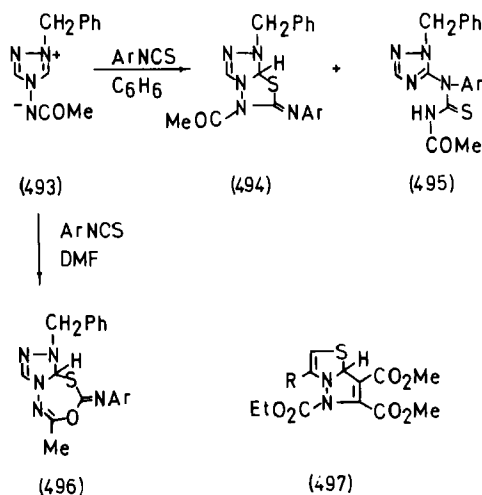
Michael addition product (489) (72BSF3974). The same compound was obtained by the action of DMAD on the authentic 4-methylamino-1,2,4-triazole. Thus, salt **477** undergoes a Dimröth rearrangement in alkaline medium to afford **488**, which reacts further with DMAD.



Reactions of 1,3-dipolarophiles with *N*-acyliminoazolum betaines proceed by a different course. The cycloaddition products either are not stabilized or are destroyed by a ruptured N—N bond. For instance, 1-alkyl-4-acylamino-1,2,4-triazolium betaines (**490**) react with an equimolar amount of DMAD to afford compounds **492**, obviously as a result of the cleavage of an N—N bond in adduct **491** (76CPB2568; 84CCC2916). The analogous reaction occurs for 3-alkyl-1-acyliminobenzimidazolium betaines (75JHC819).

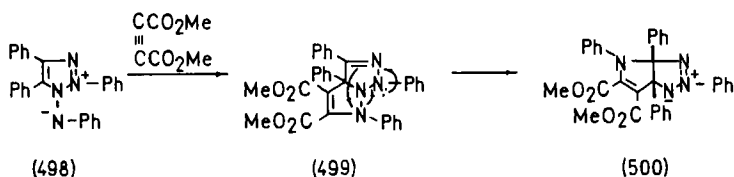


Reaction of 1-benzyl-4-acetylimino-1,2,4-triazolium (**493**) with aryl isothiocyanates in benzene yields a mixture of 1,3-cycloaddition product (**494**) and 1,5-disubstituted triazole (**495**). However, in DMF, mainly the 1,5-cycloaddition product **496** is formed (84CCC1713).



3-Ethoxycarbonylthiazolium betaine forms, with DMAD, the product of 1,3-cycloaddition (**497**) (74CPB482).

Investigated in a series of papers were the cycloadditions of activated acetylenes, ethylenes, arylisothiocyanates, carbon disulfide, and other dipolarophiles to 1-phenylimino-1,2,3-triazolium betaines; for instance, to **498** [71TL633; 72T3987; 74T445; 80AG(E)973]. The products were first

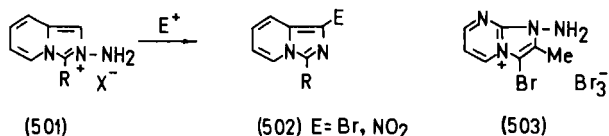


described by a structure of type **499**. However, recently Butler and co-workers using X-ray and other physico-chemical data obtained rigorous proof that the compounds are in reality pyrrolo[2,3-*d*]-1,2,3-triazole derivatives (**500**) [83CC762; 87CC1090; 89JCS(P1)371].

The cycloaddition of 1,3-diphenylnitrileimine to 1-arylideneamino-1,2,3-triazoles was investigated [88JCS(P1)3233]. This reaction occurs on the azomethine group and leads to the formation of a complex mixture of 1,2,3- and 1,2,4-triazole derivatives.

F. SUBSTITUTION REACTIONS AT RING CARBON ATOMS

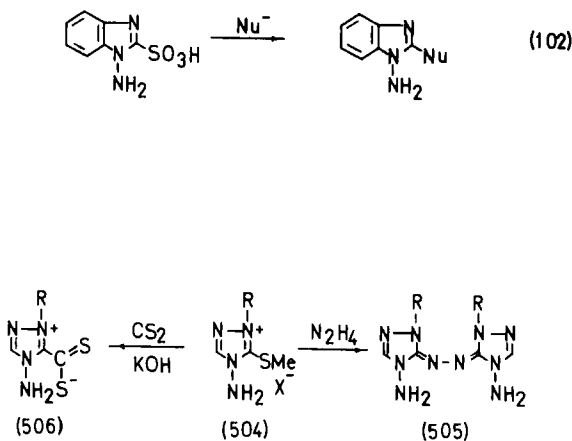
As mentioned in Section IV,D, the action of electrophilic agents on *N*-aminoazoles often leads to oxidation of the *N*-amino group or to destruction processes. In some cases, one can observe electrophilic substitution in the azoles nucleus accompanied by elimination of the *N*-amino group. For instance, under the action of bromine water or nitric acid on 2-aminoimidazo[1,5-*a*]pyridinium salts (**501**), 1-bromo- and 1-nitro-substituted derivatives (**502**) are formed [79JCS(P1)1833]. The mechanism of elimination of the amino group is unknown. Contrary to the outcome with salts **501**, the cation of 1-amino-2-methylimidazol[1,2-*a*]pyrimidinium is brominated at position 3 yielding perbromide **503**; the *N*-amino group remains untouched [77JCS(P1)78].



A successful bromination with bromine of *N*-aminopyrazoles at position 4 (88CPB3838) and 9-aminoxanthines at position 8 was reported (89KGS95). 7-Aminotheophiline is brominated at position 8 in moderate yield only in acetic acid. Under the action of bromine in water or HNO₃ in sulfuric acid, oxidation of the *N*-amino group occurs (89KGS95). 9-Aminoxanthines under the action of nitric acid form nitrates, which do not undergo nitration (89KGS95).

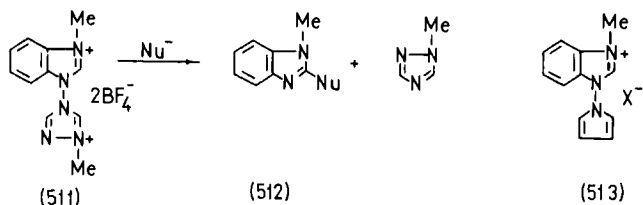
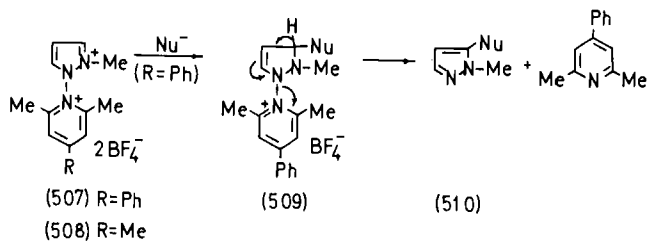
There are no examples of ring-hydrogen nucleophilic substitution for *N*-aminoazoles. However, nucleophilic substitution of such good leaving groups as SO₃H, SO₂Me or SMe is possible. This substantially enlarges the series of accessible *N*-aminoazoles. Thus, the action of ammonia, primary and secondary amines, alkali, and other nucleophiles on 1-amino-

2-benzimidazole sulfonic acid gives rise to the corresponding 2-substituted *N*-aminobenzimidazoles in good yield [Eq. (102)] (88KGS1070; 89KGS221, 89KGS1486). Similarly, the reaction of *N*-aminotriazolium salt **504** with hydrazine gives bishydrazone **505**, and betaine **506** is obtained on interaction of **504** with carbon disulfide in the presence of alkali (73JPR1131).

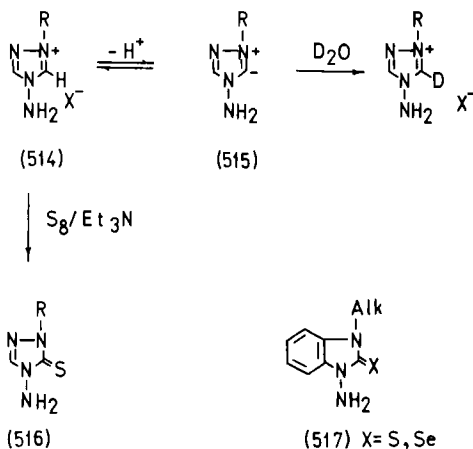


The alkoxy group in *N*-alkoxyazinium and *N*-alkoxyazolium salts activates the nucleus towards nucleophilic substitution and is easily eliminated after nucleophilic addition. De Mendoza and co-workers investigated the possibility of using *N*-azinium and *N*-azolium substituents with the same goal. The quaternary salt **507**, under the action of various nucleophiles, is converted to 1-methyl-5-*R*-pyrazoles **510** in high yield. Such a course of nucleophilic substitution at the pyrazole ring has no analogy. Supposedly, the reaction proceeds via adduct **509** stabilized by elimination of a molecule of 2,6-dimethyl-4-phenylpyridine (85TL5485). If salt **508** is used instead of **507**, nucleophilic substitution is sharply retarded. By analogy, 2-substituted 1-methylbenzimidazoles (**512**) were synthesized from bis-salt **511** [85JCS(P1)1209]. Such reactions did not succeed with mono-salts of *N,N'*-bihetaryls, for instance, with **513**.

N-Aminoazolium salts are characterized by increased CH-acidity and easily undergo basic H-D exchange. This process was investigated, for instance, with the help of the ¹H-NMR spectroscopy for 4-amino-1-*R*-1,2,4-triazolium salts (**514**) (73JPR97). By the action of sulfur on salts **514** in the presence of triethylamine, thiones **516** were obtained in a yield of 65–92% (71JPR795; 73JPR97). Under the same condition, 1-amino-3-



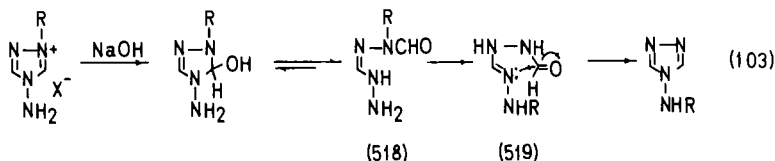
alkylbenzimidazolium salts react with sulfur and selenium, yielding thiones and selenones (**517**), respectively (90KGS1689). Supposedly, both H-D exchange and thiolation proceed with participation of ylids, for instance **515**.



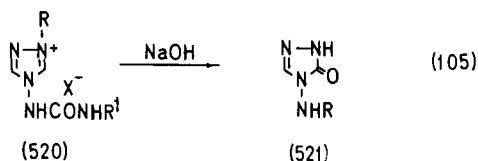
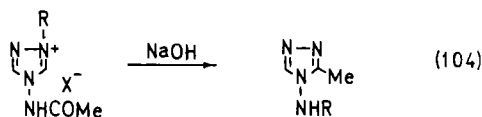
G. RING TRANSFORMATION OF N-AMINOAZOLIUM CATIONS

In a series of papers, Becker and Timpe investigated base-catalyzed transformation of 4-amino-1,2,4-triazolium salts. Thus, on heating 1-alkyl-4-aminotriazolium salts with 10% aqueous alkali, 4-alkylaminotriazoles

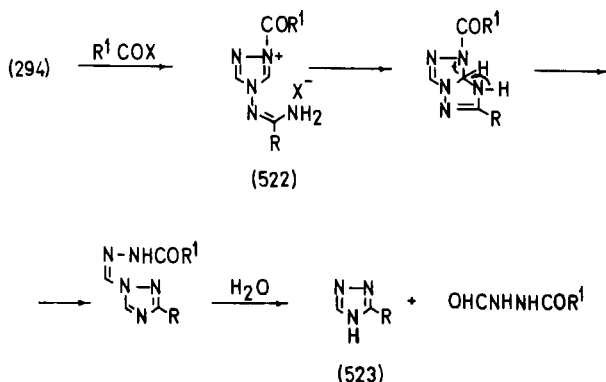
are formed in good yield [Eq. (103)] (69JPR9). For an explanation of the reaction course, one must assume a migration of the formyl group in the acyclic pseudobase to the unsubstituted amino group (**518** \rightarrow **519**).



Similar alkaline treatments of 4-acetylamino-1-alkyltriazolium (69JPR-897) and 4-ureido-1-alkyltriazolium salts (71JPR795) lead to 4-alkylamino-3-alkyltriazoles [Eq. (104)] and 4-alkylaminotriazoline-3-ones [Eq. (105)], respectively. In the latter, case, if $\text{R}' = \text{Ph}$ in **520**, 4-phenyltriazolinone is formed in low yield along with **521**.

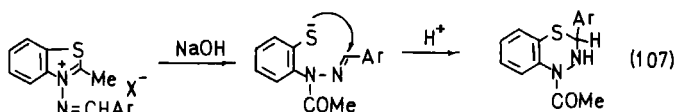
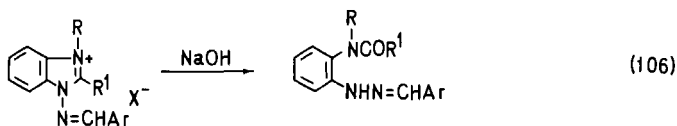


1-Acyltriazolium salts **522**, generated *in situ* from amidines **294**, are transformed to 3-substituted 1,2,4-triazoles **523** on heating in nitromethane or acetonitrile (69JPR477, 69JPR646). In this case, the presence of alkali



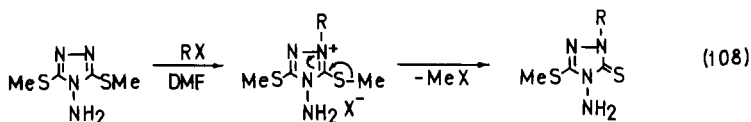
is not necessary, since the nucleophile is the amino group of the amidine fragment, which intramolecularly attacks position 3 in the triazole ring.

Salts of 1-alkyl-4-arylsulfonylamino-*s*-triazolium (70JPR1112), 1-alkyl-4-arylideneamino-*s*-triazolium (69JPR9), and 1-arylideneamino-3-alkylbenzimidazolium (75JHC225; 86KGS346) are converted to acyclic pseudobases by the action of alkalines [Eq. (106)]. Under the same conditions, 3-arylideneaminobenzothiazolium salts undergo ring enlargement, yielding benzo-1,3,4-thiadiazine derivatives [Eq. (107)] (74S126).

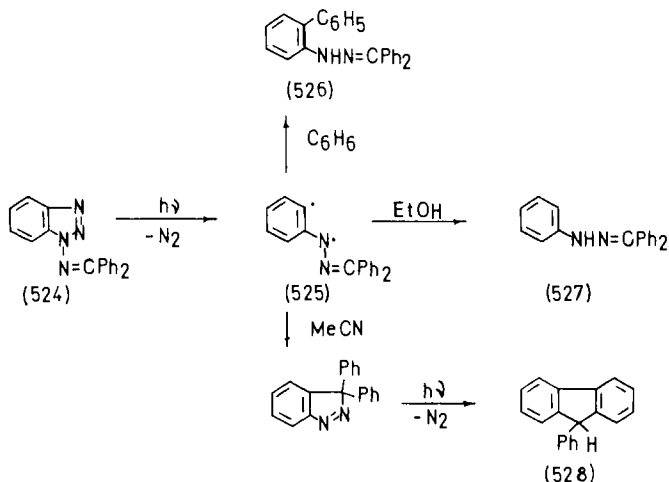


H. MISCELLANEOUS REACTIONS

4-Amino-3,5-bismethylthio-1,2,4-triazole is converted by alkylating agents in refluxing DMF into the corresponding 1-alkyl-4-amino-5-methylthiotriazoline-3-thiones [Eq. (108)] (83S414).



A series of photochemical reactions of *N*-aminoazoles was investigated. Thus, 1-aminobenzotriazole on irradiation in benzene is quantitatively transformed to diphenyl. The course of photolysis of Schiff bases **524** is strongly dependent on the solvent. Supposedly, **524** first loses a molecule of nitrogen, which results in biradical **525**. The interaction of the latter compound with benzene and ethanol yields hydrazones **526** and **527**, respectively, whereas in acetonitrile, **525** is transformed to 9-phenylfluorene (**528**) with yields of up to 80% (68JA1923).

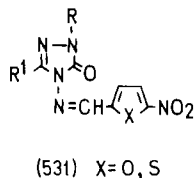
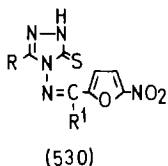
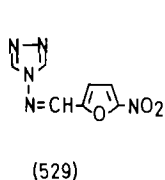


Photolysis of *N*-isopropylideneaminonaphtho[1,8-*d,e*]triazine gives 1-isopropenylnaphthalene in 60% yield (68JA1923).

V. Uses

Apparently, *N*-aminoazoles have not been found in nature. This probably accounts for the lack of interest in searching for their useful properties, such as biological activity. Consequently, only a few *N*-aminoazoles have found practical application.

It was discovered only in the middle 1950s that 4-(5-nitrofurfurylidene)amino-1,2,4-triazole (529) possesses strong bacteriostatic activity (54MI1). Under the name Furasonal, it was used in the USSR against bacterial infections (71MI1). The activity of the Schiff bases 530 and 531 against gram-positive and gram-negative bacteria [83MI2; 87MI1; 88IJC(B)683] was reported. Moderate or good activity towards various bacteria and fungi is found for 4-aminotriazoline-3-thiones, their *S*-alkyl derivatives, and also for derivatives of triasolo[3,4-*b*]-1,3,4-thiadiazole



(**446**) and triazolo-[3,4-*b*]-1,3,4 thiadiazine (**460**) (86JHC1439, 86JHC1451; 87JHC1173). Antifungal activity has been discovered for 5-nitrofurfuryl derivatives of 1-aminopyrazole and 1-aminoimidazole (88MI1). Some triazolo[3,4-*b*]-1,3,4-thiadiazines possess antihelminthic activity (83JPS45).

There are data on antidepressive, antitumor, and hypotensive actions of 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles (82JIC769); vasodilatoric, hypotensive, and cardiorespiratoric activity of 1,2,4-triazolo[4,3-*b*]-1,2,4-triazines (61FRP1248409); antidepressive, analgetic, antihistamine, and spasmolytic action of 1-amino-5-alkoxypyrazoles (76USP3944563; 81FRP2479219); and antihypertensive activity of 3,4-diamino-1,2,4-triazole and its Schiff bases (83MI1; 85MI2; 86MI1). *N*-Aminobenzimidazolones show anticonvulsive properties (85JHC1089). Salts of the 1,1'-azobenzimidazolium [74JCS(P1)1792] and 1,1'-azoimidazo[1,2-*a*]pyridinium (74USP3849557) possess short-term muscular and neuroblocker activity similar to curare. 1-Aminoxanthines display cardiotonic activity; however, this activity is weaker than that for theophiline (85YZ730).

There are no data on the anticancer activity of *N*-aminoazoles. But polycyclic compound **441**, obtained from 7,8-diaminetheophiline, is active against P-388 leukemia (87CPB4031). There are a few reports on applications of *N*-aminoazoles in agriculture. 1-Aminobenzotriazole is an insecticide and herbicide synergistic (86CC767), 1-Aminobenzimidazoles are active against fungi (73GEP2300521), and 3-amino-4-ethoxy carbonylamino-5-(2-hydroxyphenyl)-1,2,4-triazole was recommended as sweetener (70AP634). *N,N'*-Dibenzotriazolyls were suggested as possible explosives (65USP3184471, 65USP3184472). *N*-Aminopyrazoles, derivatives of pyrazolo[1,5-*b*]-1,2,4-triazole and 1,2,4-triazolo[4,3-*b*]-1,2,4-triazine, can be used in photography (61FRP1248409; 64BEP642615; 65USP3207763).

VI. Conclusion

This review demonstrates that the chemistry of *N*-aminoazoles is of great synthetic value. Probably in the future, all branches of the chemistry of *N*-aminoazoles will be developed; however, some seem more promising. These include syntheses and reactions of organic-metallo compounds of *N*-aminoazoles, investigations of the mechanism of oxidation and searches for new applications of this reaction, and the use of the *N*-amino group as a protective function. There is an interest in a possible use of *N*-aminoazoles as potential aminating agents. For a more detailed understanding of the electronic structure of *N*-aminoazoles, it is necessary to pursue the X-ray, structural, and ¹⁵N-NMR spectral investigations. Systematic investi-

gations on electrochemical oxidation and reduction of *N*-aminoazoles are also necessary.

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2,3,4-Furantriones

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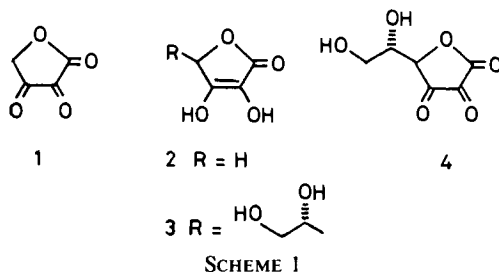
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I. Introduction

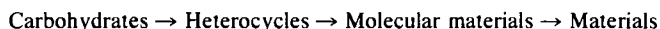
The simplest member (**1**) of the 2,3,4-furantriones is the one obtained by oxidizing the hydroxy tetrone acid (**2**) (Scheme 1). The interest in that ring system was increased after the discovery of L-ascorbic acid (**3**, vitamin C) and its oxidation product dehydro-L-ascorbic acid (DHA)¹. The latter was formulated as the traditional compound **4**, possessing the furantrione ring, but it was found to be equilibrated with other forms as will be discussed later. The role of **3** in biological systems arises from its function in the oxidation–reduction processes. The ratio of **3** with **4** may be related to cell division and therefore may have a critical role in growth regulation in addition to its use as antioxidant in foodstuffs.

The presence of three adjacent carbonyl groups in the frame of the furantrione ring explains the high chemical reactivity inherent with such molecules. Consequently it was anticipated that they could be excellent precursors for constructing heterocyclic rings either by retaining the carbon skeleton of the furanone (lactone) ring or by rearrangement via its opening. Furantriones, which possess a plethora of functional groups with chiral centers, are capable of being precursors for the asymmetric synthesis of natural products (83MI1). Moreover, those molecules possessing polyhydroxyalkyl residues could be cleaved or degraded to, for example, carbaldehyde or furfural derivatives, whose chemical modification may afford products of significant value in the applied field. Thus, 5-hydroxymethylfurfural, which is industrially available by conventional degradation of carbohydrate molecules (83MI2) offers the possibility of producing substances that compete with petroleum-derived chemicals (85CB1836; 86CB2631; 87MI3, 87MI4; 88MI7, 88MI8). It is a key substance between carbohydrate chemistry and renewable resources and the conventional industrial organic chemistry based on petroleum. Thus, such

¹ Its nomenclature and numbering of carbon atoms may be different from that used for the simple furantrione.



reaction pathways offer opportunities for converting carbohydrates as renewable resources. The concepts just discussed were (88MI7) formulated in the following equation:

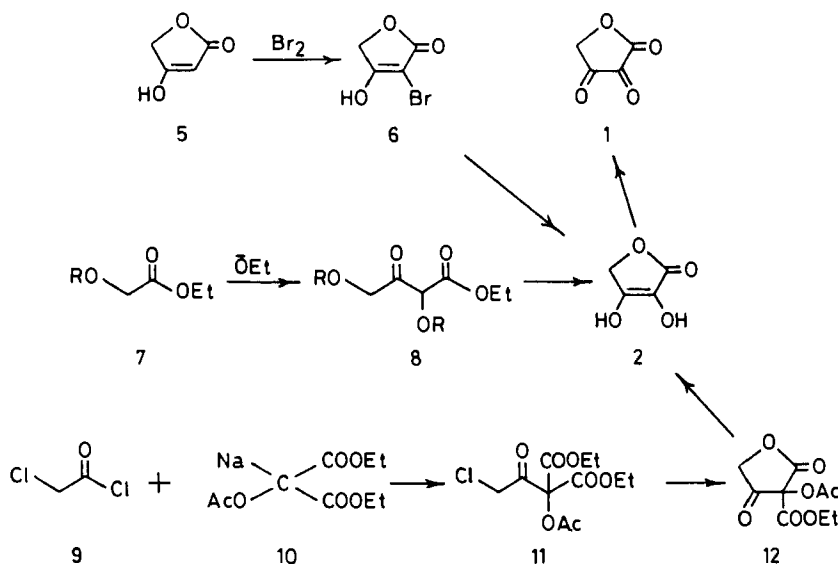


This review mostly concerns the synthesis of heterocycles from 2,3,4-furantriones (2,3-dioxobutylolactones). It can be divided into four parts, the first of which concerns the synthesis of the furantriones. The second part concerns their nitrogen derivatives, which retain the furanone ring and are mostly the starting precursors for the heterocycles in the third and fourth parts. The third and fourth parts concern the heterocycles that retain the furanone ring and those that are produced by its rearrangement, respectively.

II. Synthesis of Furantriones

The synthesis of compounds possessing the furantrione ring is based essentially on the ready oxidation of the hydroxy tetronic acids, whose synthesis, as well as that of L-ascorbic acid, were reviewed elsewhere (60QR292; 80MI2; 82MI12). Thus, compound **2** has been prepared by bromination of **5** and sequential hydrolysis of α -bromotetronic acid **6** (33CB1291) or by a Claisen ester condensation of **7** and subsequent hydrolysis of **8** (56JCS4665) (Scheme 2). It can also be prepared by the condensation of the sodioderivative of acetoxymalonic ester **10** with chloro-acetyl chloride **9** to give **11**. Ring closure of compound **11** gave **12**, which, upon hydrolysis and decarboxylation, gave **2**. Oxidation of **2** by iodine or in the presence of a trace of copper (34CB1660) affords **1**.

The 5-aryl analogues of **2** were conveniently prepared by Dahn and co-workers (54E245, 54HCA1309, 54HCA1318; 56HCA1366). The acyloin condensation of aldehyde **13** with glyoxal catalyzed by the cyanide ion

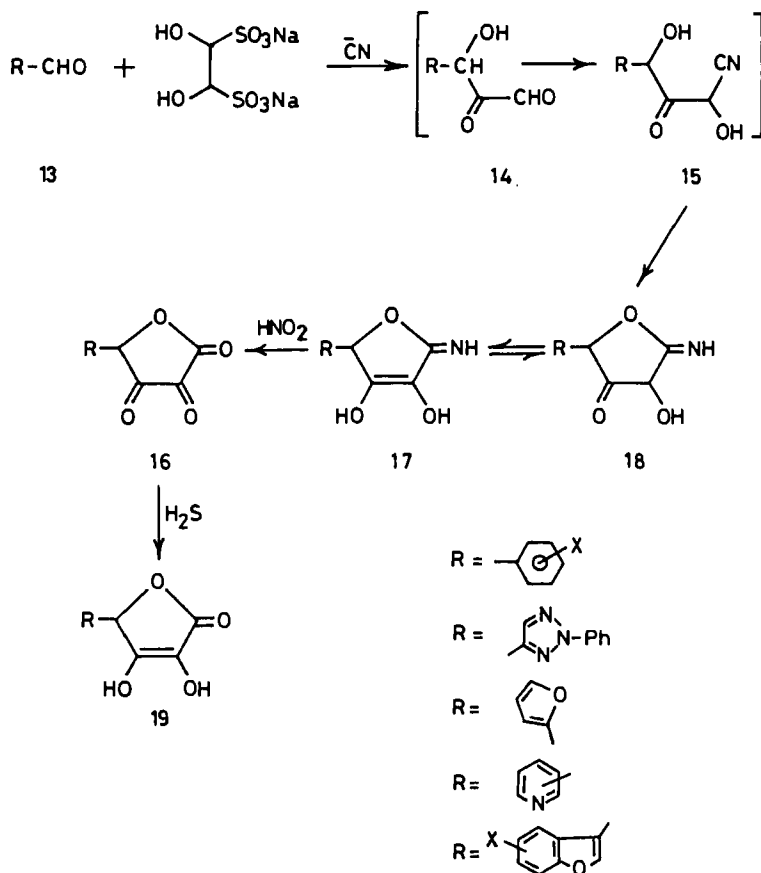


gave intermediate **14**, which cyclized to **18** via **15** (Scheme 3). Compound **18** then tautomerized to **17**. Reaction of **17** with nitrous acid gave the trioxo compound **16**, whose reduction with hydrogen sulfide gave enediol **19** (56AK489).

The previous sequence of reactions was found to be generally useful for synthesizing these types of compounds (82JMC90). El Ashry and co-workers introduced the use of this method as an approach for synthesizing novel types of C-nucleoside analogues (80MI6, 80MI9) possessing the enediol system, which is a unique feature of L-ascorbic acid. This was achieved by using heterocyclic aldehydes instead of aromatic aldehydes. Thus, 2-phenyl-1,2,3-triazole-4-carbaldehyde (80MI6) and its *p*-bromophenyl derivative (82MI5), furfuraldehyde, 2- and 4-pyridinealdehyde (54HCA1309), and 2-carbaldehyde-3-methylbenzofuran and its 5- or 7-methyl derivatives (86MI8; 82MI5; 87MI6) were used to synthesize **17**.

When the aldehyde under the previous conditions was used in molar concentration twice that of the other reactants, a slightly soluble reductone containing two aldehydes, one glyoxal, and one HCN was obtained (54E245).

The oxidation of **3** to DHA was studied in great detail and reviewed (82MI12). A variety of oxidizing agents, such as the halogens, chlorine, bromine and iodine (50JBC81; 51JA3827; 70ZPC52; 71LA152; 78ABC173),



SCHEME 3

oxygen (78ABC173), quinones (70MI1), and potassium iodate (45BJ1) were used. One of the practical methods of its preparation uses oxygen over charcoal catalyst in ethanol, methanol, or water (83ABC607). However, ethanol was found to be the best. The oxidation may have occurred through the formation of a free radical intermediate, monodehydro-L-ascorbic acid, whose chemistry is reviewed (82MI1).

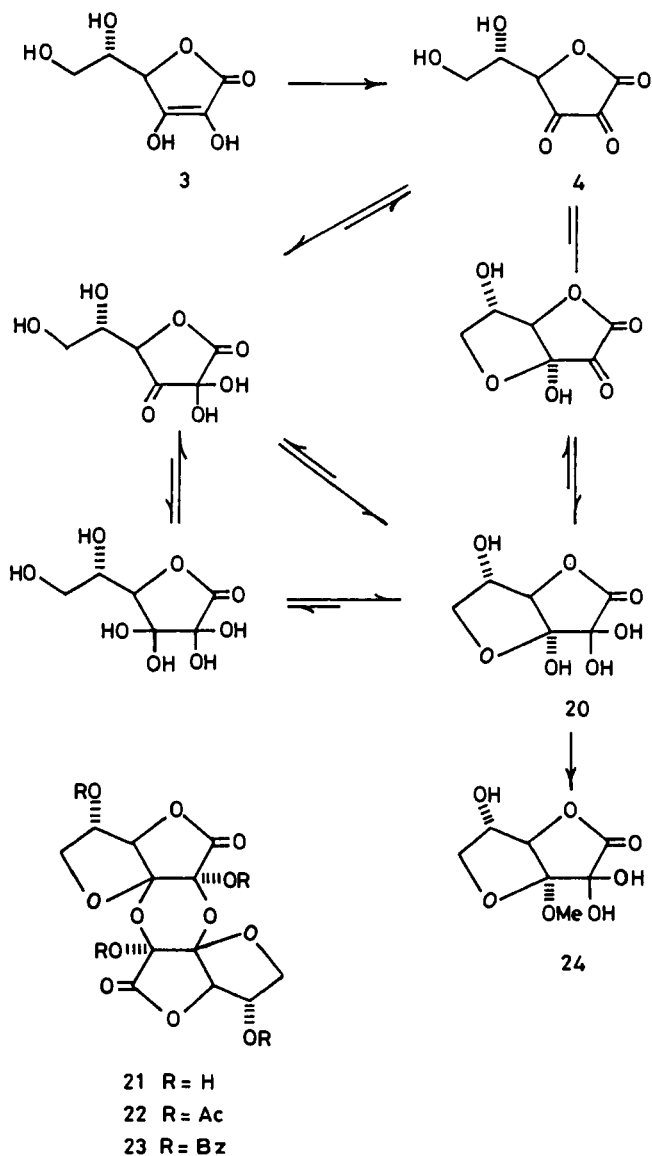
One electron oxidation of **3** and its analogues or derivatives was investigated by electron spin resonance (ESR). Two types of spectra corresponding to an anion radical and a neutral species (71CPB718; 72CPB2651) were observed when a $\text{Ti}^{3+}/\text{H}_2\text{O}_2$ system was used as the oxidizing agent. The *ab initio* self-consistent field (SCF) method was used to study the electronic structure of ascorbic acid and its metabolites. The bulk of the calculations

involved the use of α -hydroxytetronic acid as a model for ascorbic acid and the use of related compounds as models for the ascorbyl radical and dehydroascorbic acid (81MI9).

The oxidation of **3** and its phenyl analogue **19** by nitrous acid to give the corresponding dehydro derivatives and NO (60HCA287, 60HCA294, 60HCA303, 60HCA310, 60HCA317, 60HCA320) was carried out at various pH values in the presence of N_3^- and HN_3 . A considerable decrease in the rate of reaction was observed. Both **3** and **19** possessed a stabilized enediol group which was smoothly oxidized by mild oxidants such as the typical monoelectron acceptors (Fe^{3+} , Ag^{1+} , Cu^{2+} , iodine). This suggests a stepwise transfer of the two electrons and the formation of an extremely reactive intermediate. When oxidized by HNO_2 (prepared from NaNO_2 and HClO_4 or H_2SO_4) under various conditions, the same final product arose, although some differentiation among the intermediate reactions was achieved by restricting the pH range. These phenomena are explained either by the action of various nitrosation agents of different reactivity formed from HNO_2 , namely $\text{NO}^+ > \text{H}_2\text{NO}_2^+ > \text{N}_2\text{O}_3$, or by the different ionization of **3** and **19** at pH 2 and pH 4, where a considerable $[\text{Red}^-]$ is formed that is increasingly susceptible to autooxidation.

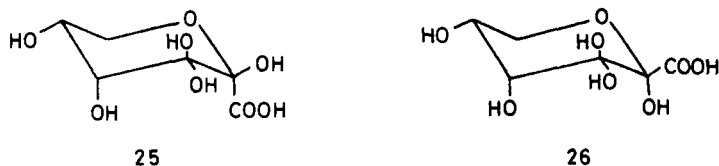
The structure of DHA, which is the first chemically stable product in the oxidation of **3**, was first postulated to be 2,3-diketolactone **4**, with possibly one or more of the keto groups hydrated (Scheme 4). However, studies based on NMR and ESR spectroscopies and X-ray crystallography led to a better understanding of its structure [48JCS158; 70LA206; 72AX(B)916; 75MI2; 76MI6; 77T1587, 77ZN(B)562; 79ACS(B)503; 80ACS(B)285; 82MI10, 82MI12]. The data indicated that an equilibrium of various structures probably exists, with the hydrated hemiketal **20** being the favored form. This was verified by studying the ^{13}C -NMR spectrum of DHA, where C-6 appeared more downfield than its precursor **3**, suggesting its involvement in a hemiketal as in **20**. The assigned shift for C-2 is further upfield than would be expected if C-2 were a keto group, which indicates hydration at that carbon.

Although **20** could not be isolated in a crystalline state in the monomeric form, it can be trapped as its stable crystalline derivative **24**. On the other hand, compound **20** can be crystallized from nitromethane as a symmetric dimer **21** comprising a system of five fused rings (70ZPC52, 70ZPC56). This dimer can also be obtained by the oxidation of **3** with *p*-benzoquinone, chloranil, or mercuric acetate in *N,N*-dimethylacetamide or dimethyl sulfoxide (DMSO) followed by precipitation by an organic acid. The dimeric structure is directly demonstrated by measuring the time dependent optical rotation. The dimer's acetylation and benzylation gave **22** and **23**, respectively.



SCHEME 4

The structure of dehydroisoascorbic acid isomer (81MI5) in solution is only partially similar to **20**. In dimethylformamide (DMF), the preponderant species is a symmetric dimer. In water, significant differences are observed. In fresh aqueous solutions, it is present as bicyclic lactone, but



SCHEME 5

with time, it is transformed irreversibly into approximately equal amounts of two pyranose anomers **25** and **26** (Scheme 5). This difference from **20** is probably caused by strain in the lactone ring due to the proximity of oxygens 4 and 5 after formation of the furanoid ring. In water, this leads to opening of the lactone ring before the furanoid ring.

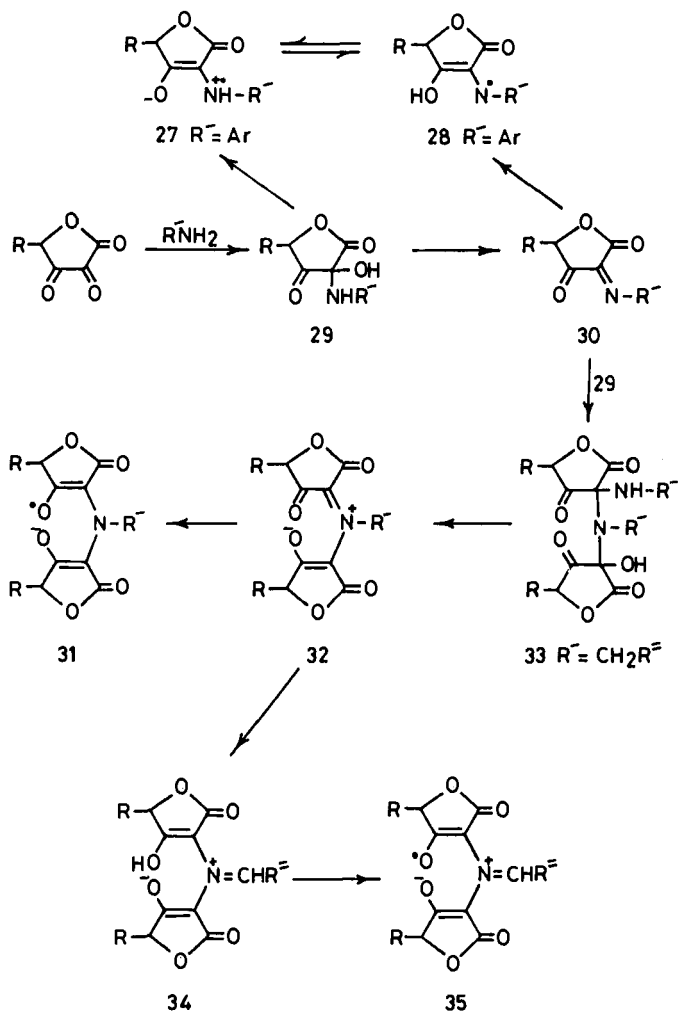
III. Nitrogen Derivatives of Furantriones

A. REACTION WITH AMINES

Much work has been directed towards the scope of the Maillard and browning reactions involving furantrione and its derivatives. It has been reported that **3** undergoes C-2-C-3, C-3-C-4, and C-4-C-5 cleavage reactions in the presence of amines or amino acids and gives various aminocarbonyl reaction products, including amino derivatives of DHA, 2-deoxy ascorbic acid, oxalic acid, urea, and isatin (76YZ608, 76YZ932).

The reaction of a primary alkyl or aralkylamine with DHA led to the development of a yellow color which changed, on heating, to wine red and then brown. As soon as the heating started, characteristic intense ESR signals were observed; a detailed study of the reaction was done (75MI3; 76ABC1209; 77MI5; 78ABC809). The radical intermediates were fairly stable and are blue. Their color turned to red on oxidation with *p*-benzoquinone. Examination of the ESR spectra of the blue-colored radicals indicated they have a common basic composition of two units of DHA and one unit of the respective amine whose alkyl residue is present in the product. A possible reaction mechanism was proposed in which one molecule of amine produces Schiff bases **30** via the intermediate carbinolamine **29** (Scheme 6). Reaction of **29** and **30** afforded **32** via **33**, which, through some electron transfer and oxidation or reduction processes, gave the radicals **31** and **35** via **34**.

The reaction of DHA with primary amines having only one or no α -protons, such as isopropyl-, *sec*-butyl-, or *tert*-butylamine, gave spectra



SCHEME 6

similar to those detected in the reaction of sugar with amines. The reaction of secondary or tertiary amines with DHA did not show characteristic ESR spectra other than a signal which is probably similar to that of the reduction of DHA in alkaline solution and corresponds to that of the ascorbyl free radical.

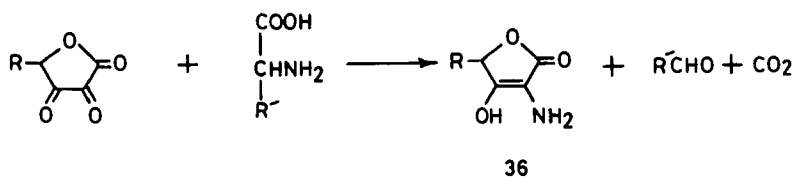
When an equimolar mixture of DHA and an aromatic amine was heated, a yellow coloration first developed which changed to green, then to red

within a few minutes and gradually to dark brown. A characteristic ESR signal was observed within a few minutes after heating. An explanation of the mechanism of the radical formation in such reactions is analogous to the reaction of ninhydrin with aromatic amines. The radical products can be given structure **27** or **28**, both of which are composed of one unit of the aromatic amine. The absence of substituents at the ortho positions was assumed to favor the formation of radical **27**. When only one of the ortho positions was substituted, the formation of radical **28** was dominant, and when both of the ortho positions were substituted, both types of the products were detected.

The decomposition products and browning activities of the 5-phenyl furantrione and its phenylhydrazone was studied during their reaction with *p*-tolylamine (73YZ278). The browning activities of the phenyl analogue were much stronger than DHA and required air for its decomposition, while the furantrione decomposed in nitrogen as well as in air. A variety of products were isolated and assumed to be due to a radical cleavage of the lactone ring to one to three carbon fragments.

B. REACTION WITH AMINO ACIDS

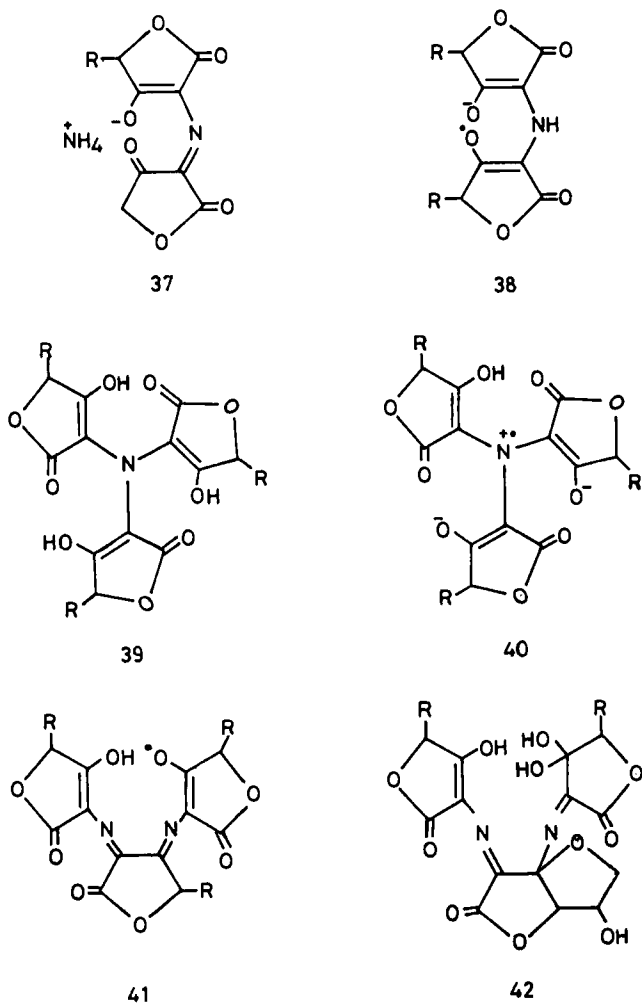
The well-known reaction of DHA with amino acids develops a red pigment. The amino acids are quickly deaminated with the formation of **36** and an aldehyde having one carbon atom less than the original acid—a typical Strecker degradation (Scheme 7). The aldehydes are isolated as dimedone derivatives and are useful for identifying the amino acids. In the presence of Cu and UV light, the rate of the deamination increases. The red color has been used to detect amino acids by paper chromatography (64MI1; 68MI3). The red pigment was found to be an intermediate in the browning reaction and is related to colorations that appear during the processing and storage of some foods, which consequently causes their deterioration (73ABC1471, 73ABC2935; 74CL125, 74CL1193; 76MI5; 78ABC2239; 79TL4467; 80EA605, 81ABC711; 82ABC1199; 83ABC1003, 83ABC1955). Its structure was proposed as **37** (73MI2, 73MI3;



SCHEME 7

74ABC1981, 74MI3; 86ABC3193). This structure was confirmed by NMR and ESR spectra.

The ESR spectrum of the reaction of DHA and amino acids showed the presence of two sets of signals. One of these sets is identical in each spectrum and corresponds to a blue radical species that is oxidized with air to a red one. The product was identified as tris(2-deoxy-2-L-ascorbyl)amine **39**. It has a three-fold symmetric structure around one nitrogen atom originating from the amino acid (81ABC711). The red



SCHEME 8

pigment was found to be the oxidized form of bis(2-deoxy-2-L-ascorbyl) amine **37**, which resulted from the elimination of one molecule of ascorbic acid (Scheme 8).

The previous interpretation is in complete accord with the results of an electrochemical study (80EA605) which has demonstrated that **39** undergoes two reversible one-electron transfer steps. The first step occurs through a dianion. Its product is the unusually stable blue anion radical **40** and is the second step via this radical species to some oxidation product such as **38**, which is unstable and is slowly converted to the red pigment **37**. Reaction of **36** with **37** or DHA produced the yellow pigment **42**, whose one-electron reduction gave the radical **41**. Thus, fairly stable free-radical products could easily be formed by the reaction of DHA and α -amino acids, which are generally present in foods and biological systems and are of interest because of possible antioxidative action and because of various important effects of **3** in biological systems.

Volatile products from the reaction of DHA with ammonia and glycine were identified as methyl, 2,5-dimethyl, trimethyl, and tetramethyl pyrazine as well as 2,5-dimethyl-3-ethyl pyrazine (77MI6).

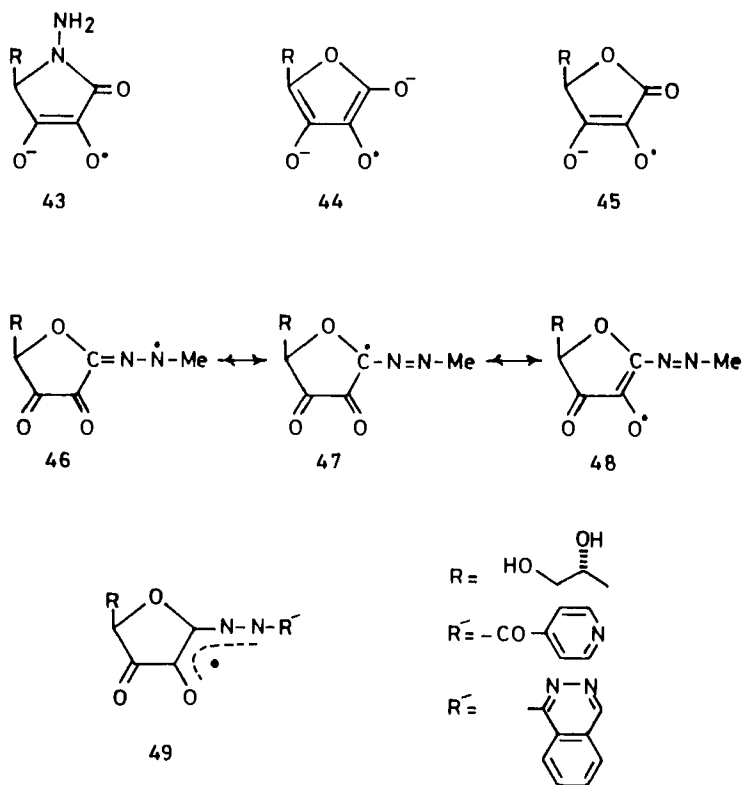
C. REACTION WITH HYDRAZINES

The importance of the bishydrazones of furantriones lies primarily in obtaining crystalline derivatives that are needed for their identification and to act as precursors for heterocyclic compounds. Thus, these materials can be traced back to the early work on hydroxy tetronic acid and vitamin C, where a number of the corresponding bishydrazones were prepared.

1. *Formation of Free Radical Species*

It has been reported (69TL5005) that an ESR spectrum was observed during the autooxidation of the aqueous alkaline solution of **3** in the presence of hydrazine. This spectrum was said to be due to structure **43**, based on the structure of monodehydro-L-ascorbic (**44**) (Scheme 9). When that structure was revised to **45**, it was deduced that pyrrole ring structures **43** were not formed (74CPB1417). Further studies of the reaction in an aerobic alkaline aqueous solution gave rise to some radical intermediates.

The ESR parameters of the radical species obtained (75CPB1516) from the reaction of methylhydrazine with different analogues have similar characteristics with respect to the hyperfine splittings. Consequently, the basic structure of these radical species can be considered the same, namely **46** \leftrightarrow **47** \leftrightarrow **48**, the high resonance stabilization of which contributed to



SCHEME 9

their stability. These radicals were neither produced under nitrogen nor produced rapidly in the presence of air. They were not found in the acidic and aerobic solution, but were immediately observed at pH 9. Consequently, it was deduced that the reaction takes place rather slowly to form some diamagnetic intermediate, i.e., a precursor of the radical species. The formation of such an intermediate is probably associated with the condensation of **3** with hydrazine derivatives. The intermediate is then quickly oxidized in the weak alkaline solution to yield the radical species. The oxidation took place also with a ceric salt or potassium ferricyanide. The reaction route may also have proceeded through a precursor that was inactive to ESR, but after several hours exposure to air, the mixture turned purple and became active to ESR. Compound **3** and isoniazide or apresoline produced fairly stable free-radical intermediates when present together in aqueous alkaline solutions. In view of the similarities in the

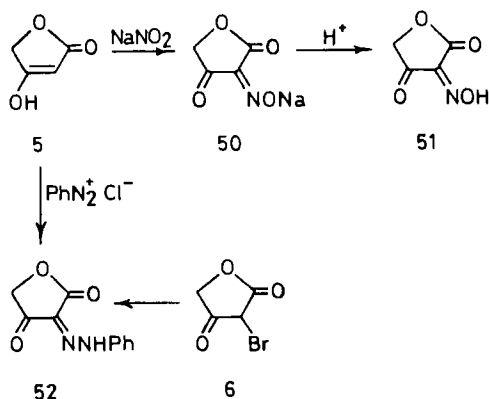
ESR parameters to the radical from **3** and hydrazine, the same skeletal structure was assumed and represented as **49** (75CPB1632).

2. Formation and Tautomerism of Monohydrazones

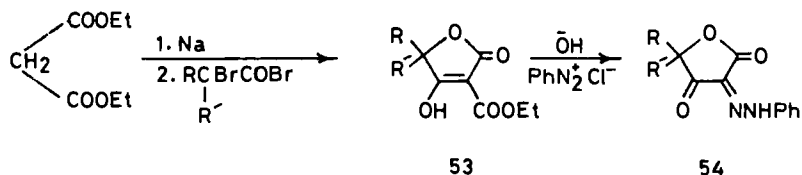
Tetronic acids that are not substituted at the α -position gave, on treatment with sodium nitrite, a purple color due to the formation of sodium salts of hydroximinotetronic acids **50**, whose acidification gave the yellow oxime **51** [1896LA(291)231] (Scheme 10). Coupling of benzene diazonium chloride with tetronic acid in alkaline solution gave the hydrazone **52**, which gave the corresponding oxime and gave no color with ferric chloride [1900LA(312)133]. Treatment of the bromolactone **6** with diazonium salts gave **52** (74MI4). Reaction of the α -ethoxycarbonyllactones **53** with benzenediazonium salt gave the monohydrazone **54** (55RTC1217) (Scheme 11). Lactones **53** are readily available from malonic esters by reaction with α -bromoacyl bromides.

The first synthesis of phenylhydrazone **56** by the reaction of benzene diazonium chloride on **57** (37N158, 37ZPC34) was similar to that used for tetronic acid derivatives. The later could be prepared from **55** through the sequence shown in Scheme 12 (35HCA602; 36CB879).

Subsequently, the reaction of DHA with 1-acetyl-2-phenyl-hydrazone was used to form **56** (70MI3; 76MI3). Although a controlled reaction of **20** with phenylhydrazine did not afford **56**, the corresponding substituted phenylhydrazones **60** could be obtained by this method (Scheme 13) [76AX(B)448; 77MI1, 77MI4; 80ACS(B)429; 84MI1]. This method was used, however, to synthesize the D-*erythro*-analogue of **56** (73YZ304). The



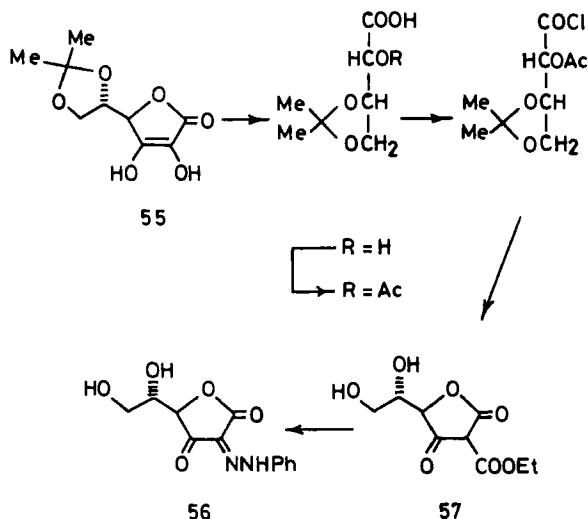
SCHEME 10



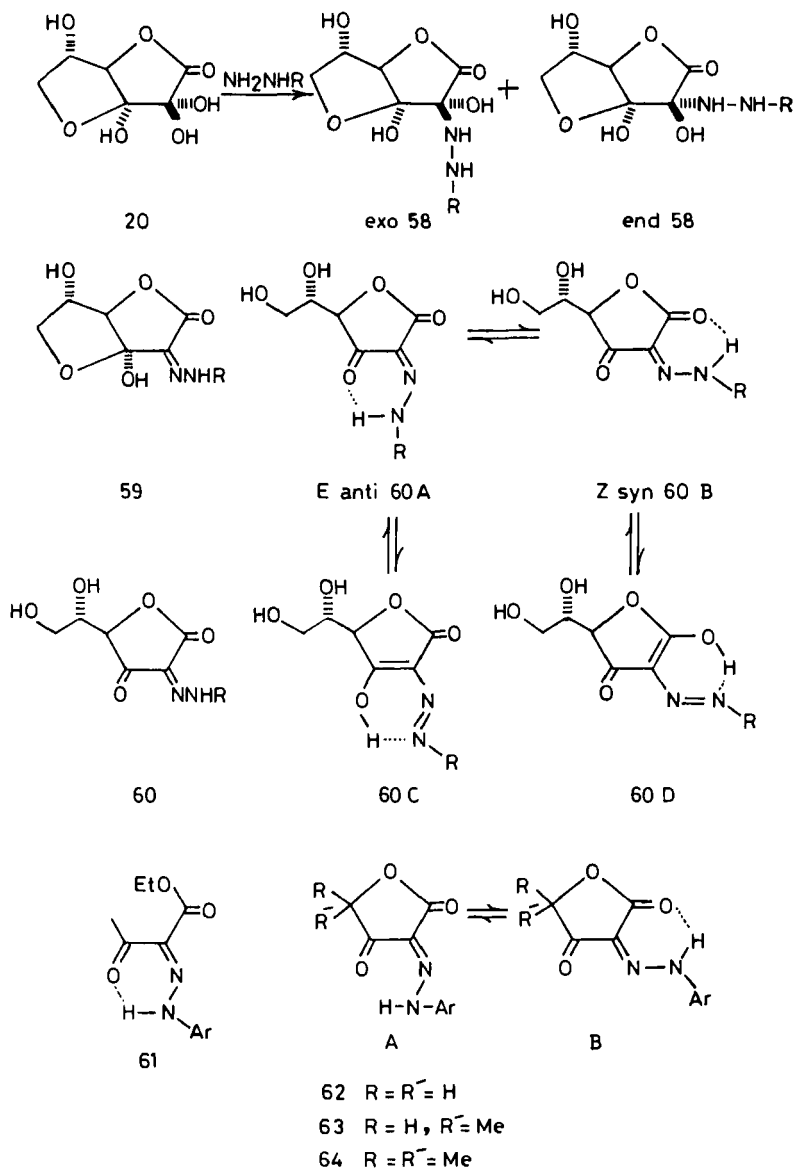
SCHEME 11

regioselective formation of the arylhydrazones, at C-2 of **20** and its *D-erythro*-analogue, can be effected with an acetone aryl-hydrazone in an aqueous medium (88MI4). The reaction is general, and the acetone liberated does not interfere with the isolation of the product. Although the C-2 carbonyl of DHA is the most reactive, the regioselectivity was enhanced by the existence of DHA mainly in the bicyclic form, whose preponderance immediately after the oxidation of **3** was confirmed. In spite of the anticipated formation of intermediate **58**, the products isolated were **60** but not **59**.

A study of the reaction pathway was done by ^{13}C spectroscopy for a stoichiometric amount of the arylhydrazine and DHA in a solution of *N,N*-dimethylformamide [80ACS(B)429]. The reaction mixture immediately contained *exo* and *endo* diastereomeric hydrazines **58** in equilibrium in unequal amounts. These intermediates are transformed to hydrazones **60**,



SCHEME 12



SCHEME 13

where the NH group, hence, can establish hydrogen bonds to either O-1 or O-3. The structure of **60B**, where the NH weakly hydrogen bonds to O-1 was supported by X-ray crystallography of the *p*-bromophenyl analogue [76AX(B)448]. The lactone ring is in the envelope conformation and is

almost coplanar with the phenylhydrazone part. Whereas hydrogen bonding is intramolecular and tends to stabilize the planar hydrazine group, the O(6)—H . . . O(3) and O(5)—H . . . O(6) bonds combine to form and reinforce a helical interaction. The only participants are neighboring ascorbate moieties that are arranged head-to-head across screw axes. This leads to piles of symmetry-related molecules that have no obvious interaction with other piles, except for van der Waals forces [76AX(B)448].

The bond distances in the hydrazone group indicated a considerable π -electron delocalization in the system because of the contribution of resonance structure, which are energetically preferred to bicyclic system **59**. It was then concluded that a disruption of the furanoid ring follows the introduction of a hydrazone residue at C-2, which induces a π -electron delocalization in the system. This was due to the sp^2 hybridization at C-3, which precludes the necessary fourth valence for ring formation (82MI9).

^{13}C -NMR spectroscopy was used to study the tautomerism of compounds **60**–**64**. It is anticipated that a marked difference exists between the tautomeric pairs (e.g., **60A** and **60C**) in the chemical shifts of the aryl carbons, as suggested by comparison of the spectra of some model compounds such as azobenzene, acetone phenylhydrazone, and acetophenone phenylhydrazone (81JHC719). The chemical shifts are those of phenylhydrazones and are incompatible with the presence of a phenylazo group. Consequently, the hydrazone of furantriones exists in just two tautomeric forms. The tetronic acid derivatives exist in an almost equal ratio (55 : 45) of syn and anti configurations (81JHC719). However, those of the corresponding acyclic analogues, 3-ketoesters, are usually represented as the hydrogen bonded anti tautomer **61** (59SA20; 66BSF2981; 76JIC1156; 79T2013). On the other hand, that of ascorbic acid exists in a single tautomeric form **60B** [79ACS(B)503] in the crystalline state, as confirmed by the X-ray analysis [76AX(B)448]. Its ^{13}C - and ^1H -NMR spectra showed that it exists in solution in a single configuration, presumably the syn isomer.

This apparent contradiction in the tautomeric population of each tautomer in the different hydrazones was attributed to the presence of the dihydroxyethyl group on C-4, a situation which prohibits the interconversion on going from solid state to solution. This may be due to the involvement of C-3 and C-1 in intermolecular hydrogen bonding with one of the dihydroxy ethyl groups and the phenylhydrazono group, respectively. This type of hydrogen bonding prohibits the interconversion from tautomers of type B to A because the carbonyl of C-3 is not free to accept another hydrogen bond and consequently stabilizes the crystalline state. However, measuring the ^{13}C -NMR spectra of **60** at a lower temperature showed the presence of two isomers [80ACS(B)429]. Only at temperatures

higher than -10°C , is the rate of interconversion of the two isomers sufficiently fast to average out the differences in chemical shifts between them. The standard free-energy difference (ΔG) between the two isomers is found to be 0.7 ± 0.2 KJ/mol, and the free-energy barrier ($\Delta G^{\#}$) is 62 ± 2 KJ/mol. The most stable isomer has the same structure as observed for the molecule in the crystalline state. The Hückel molecular orbital (HMO) method that has been used to study the tautomerism of mono and bishydrazones is in agreement with the spectral results (82MI7).

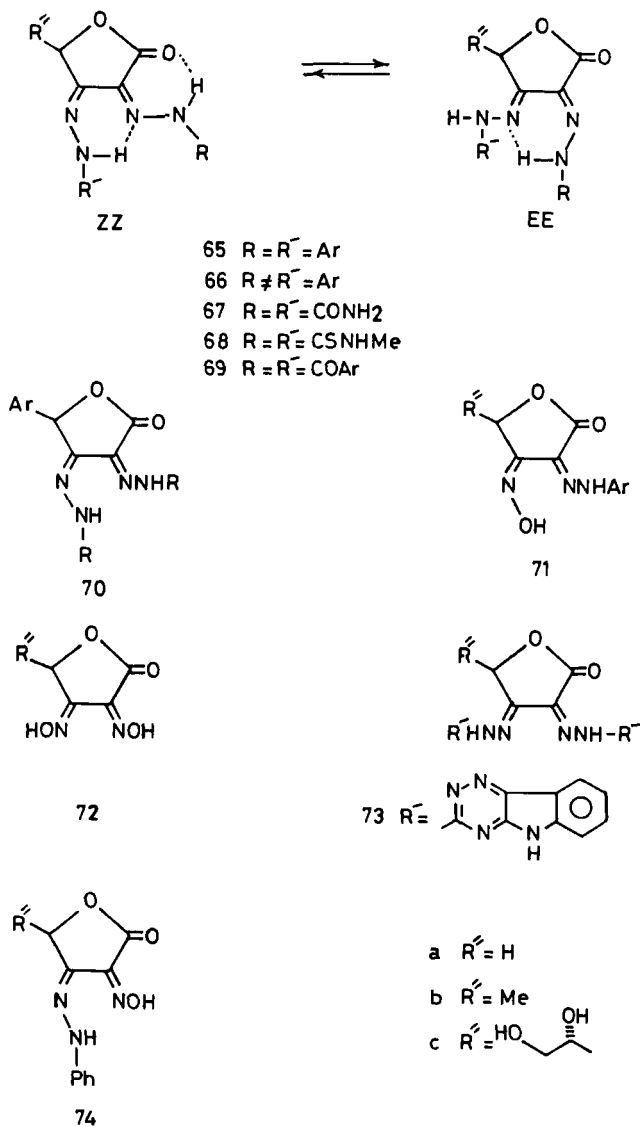
3. Formation and Tautomerism of Bishydrazones

The reaction of DHA and its analogues with hydrazines readily gave the corresponding bishydrazones. The 2,4-dinitro-phenylhydrazine derivative of DHA is widely used to determine ascorbic acid by spectrophotometry (43JBC399; 44JBC511; 61ANY277). Other components, for example, those in foodstuffs, may react with the reagent, but to be more specific for DHA, the reaction should be conducted at lower temperatures. Paper (67MI3), thin-layer (67MI1; 72MI1), and column chromatography (61BJ459) have been used to separate the bishydrazone from interfering hydrazones, but these methods are rather tedious. A high-performance liquid chromatography procedure was used for its analysis (81MI8; 83MI7).

Other bishydrazones with various substituents on the phenyl ring as well as compounds related to sulfa drugs were prepared (33JCS1270; 43MI1; 78MI4; 85MI2; 86MI6, 86MI10, 86ZC249). The corresponding bis-semicarbazones **67** (64CR587; 66BSF522), bisthiosemicarbazones **68** (74MI1), and bisacylhydrazones **69** (34MI1; 77MI2) were prepared. Similarly, derivatives **70** from the phenyl and triazolyl analogues were also prepared [54HCA1318, 54HCA1325; 55RTC1217, 55RTC1227, 55RTC1229; 77JHC927, 77MI2; 78PHA709; 81MI4, 81PHA509, 81PHA751; 85IJC(B)268]. Derivatives **73** could also be prepared from the reaction with the corresponding hydrazino-triazine.

Mixed bishydrazones were prepared by reacting the monohydrazones with another type of hydrazine to give **66** or with hydroxylamine to give **71**. They can also be prepared by reacting the oxime with hydrazine to give **74** (77ACH409; 79S977) (Scheme 14).

Three points are subjects of controversy. The first is the structure of the hydrazine residue. Is it a bishydrazone, bishydrazide, or an azohydrazone? The second point concerns the size of the lactone ring. The third point concerns the type of hydrogen bonding. The controversy is a consequence of obtaining a variety of derivatives from the reaction mixture, including its first synthesis (33JCS1270; 34CB1750; 37CB1862; 47HCA742; 52AK369; 56CR607; 67MI2). The present situation is that the bishydrazone



SCHEME 14

structure **65** is the one assigned for the product, which is sometimes contaminated with an orange product that is a pyrazolinedione resulting from the rearrangement of **65**. Moreover, the bishydrazone exists in two forms: red and orange. These two forms can be readily isolated for the *D-erythro*-analogue, whereas those of the *L-threo*-analogue could only be

isolated for the corresponding derivatives. The bis(phenylhydrazone) of the *L-threo*-analogue existed only in the red form. However, its orange form was isolated by crystallization from pyridine; it contains a pyridine molecule (unpublished results). Moreover, in solution, the orange form was detected by NMR spectroscopy.

The infrared spectra of the red osazone showed a lactone carbonyl at $\sim 1740\text{ cm}^{-1}$, whose low value was at first thought to be due to a lactone ring of different size [68JCS(C)2247, 68MI1]. It was later discovered that hydrogen bonding was the reason (88G617). On the other hand, the orange form showed the lactone carbonyl at $\sim 1780\text{ cm}^{-1}$. The IR spectrum of the red form of the *D-erythro* analogue showed two bands at 1735 and 1765 cm^{-1} in DMSO solution. With time, the former almost disappeared, while the later became intense. In dioxan solution, the transformation proceeded to about 60% (73YZ304).

Further evidence for these phenomena was provided by the UV data of compounds **65a** and **65b**. Compounds **74** and **72**, which appeared as **65c**, showed a hypsochromic shift of the high wave-length absorption on standing, corresponding to the conversion of dichelated form ZZ to monochelated form EE (80T2955). Compound **71** displayed a constant UV absorption, on standing, in agreement with the unique EE-configuration. The notably high values of the visible absorption maxima strongly suggest a chelated ring involving a phenylhydrazone group in EE and ZZ osazones **65** (444 and 468 nm), ZZ hydrazones **74** (396 nm), and EE hydrazones **71** (383 nm), as compared with glucose osazone (390 nm). These high absorption maxima are due to the presence of a five membered lactone ring adjacent to the chelated system, and not to a phenylazo group.

The ^1H -NMR spectra of the bishydrazones showed a characteristic feature. An initial spectrum of the red form in DMSO-d_6 showed the two NH as two resonances (at ~ 10.9 and 12.0 ppm) that diminished in intensity as a new pair of signals began to appear at ~ 10.3 and 12.5 ppm (70T3833). A parallel change was also observed for H-4. Inspection of the spectra of the acetates in CDCl_3 solution indicated the presence of only the red form, whose NH's appeared at ~ 10.9 and 12.0 ppm (88G617).

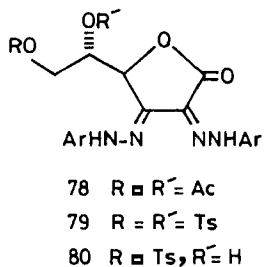
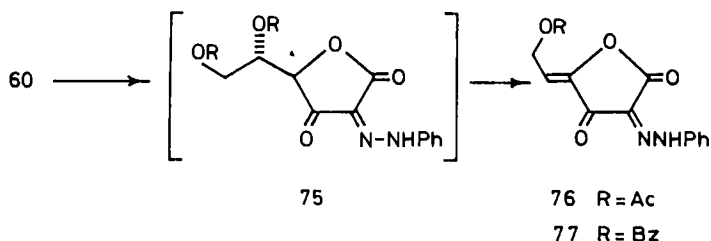
^{13}C -NMR spectra **65b,c** and those of glucose osazone support a possible nonclassical aromatic system (80T2955). Closely related shifts for the C-2, C-3, and C-4 carbon atoms provide additional evidence for the 1,4-lactone structure of ascorbic acid osazone. The structural change of ZZ to an EE-configuration in DMSO for **65a** and **65b** is more rapid than for **65c**. However, the spectra of **74a,b** and **72a,b** revealed marked differences. Unlike the case of compounds **65**, they do exist in the solid state or in chloroform in the unique ZZ-configuration, which can be estimated to be about 50%. In contrast, compound **71** in chloroform showed only an EE-

configuration. The conversion of the *ZZ* to the *EE*-configuration in basic solvents was attributed to mutarotation. A similar geometric isomerization was also noticed for **65a,b**.

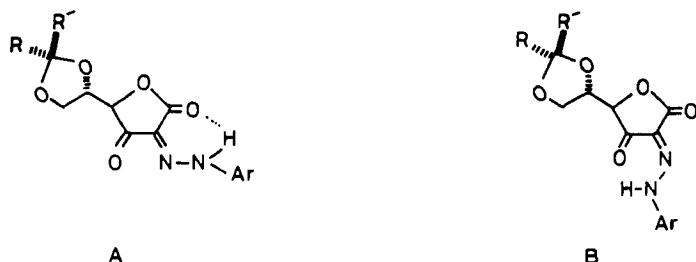
Roberts, who pointed out the difference in the chemical behavior of ascorbic acid and sugar osazones, preferred a 3-phenylhydrazino-4-phenylazo-5*H*-furan-2-one structure, which he supported by its remarkably high UV absorption [79JCS(P1)603]. However, this type of structure was ruled out by the ^{13}C -NMR spectra.

4. Acylation and Acetalation of Mono- and Bishydrazones

Acetylation of the monohydrazones **60** with acetic anhydride in pyridine did not give the expected di-*O*-acetyl derivative **75**, but elimination of an acetic acid molecule took place to give 5-(2-acetoxyethylidene)tetrahydrofurantrione 3-phenylhydrazone **76** (70MI3) (Scheme 15). The same compound was similarly obtained from the corresponding *D-erythro* isomer (73YZ304). Benzoylation caused a similar elimination to give **77**. On the other hand, acetylation of the bishydrazones gave the corresponding di-*O*-acetyl derivative **78**. Tosylation of **65c** gave the di-*O*-tosyl derivative **79**, whereas its selective tosylation gave **80** (70MI3).



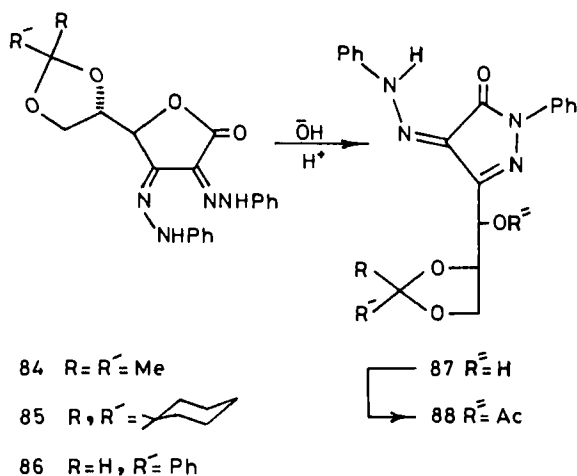
SCHEME 15



- 81 $R = R' = \text{Me}$
 82 $R, R' =$
 83a $R = \text{H}, R' = \text{Ph}$
 83b $R = \text{Ph}, R' = \text{H}$

SCHEME 16

Acetalation of monohydrazone **60** gave **81–83** (Scheme 16). The ^1H -NMR spectrum of **81** showed a chemical shift difference for the two methyl groups, agreeing with the shift rule of El Ashry (86CC1024). The previous discussion on the isomerism of hydrazones **60** indicated the possibility of their existence in two geometric isomers, particularly in solution. In the solid state, it exists in one form. However, its isopropylidene derivative was found to exist in two forms in the solid state and in solution. Similarly, the cyclohexylidene **82** exists in both forms. On the other hand, benzyli-



SCHEME 17

dene **83** exists as a mixture of four species: two diastereoisomers (**83a** and **83b**) and two geometric isomers A and B (unpublished results).

The synthesis of the isopropylidene **84**, cyclohexylidene **85**, and benzyli-dene **86** acetals of the osazones **65c** provided confirmation of the size of their lactone rings (86MI3) (Scheme 17). This was done by the re-arrangement of the lactone ring via its opening to give **87**, which, upon acetylation of the resulting hydroxyl group, gave **88**. A comparative study of the shift of the protons on the carbon skeleton by ^1H -NMR spectroscopy indicated the location of the lactone ring. Although the acetates **78** exist in only one form [68JCS(C)2247], the corresponding isopropylidene exists in the two forms ZZ and EE [88JCS(P1)133].

5. Complexes of Hydrazones

Few reports concern complexes of the hydrazones of furantriones. Thus, reaction of 3-phenylhydrazones-5-methyltetronic acid **54** and 3,4-bis(phenylhydrazones)-5-methyl tetronic acid **65b** with *trans*-[Pd(NH₃)₂] gave complexes whose analytical results were consistent with the formulae [Pd(**54**)₂] and [Pd(**65b**)₂(NH₃)₂], respectively (83MI6).

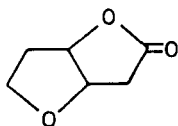
When the bisbenzoylhydrazone **69** was treated with an ethanolic solution of cupric chloride, it probably gave a complex that decomposed readily, upon heating or standing at room temperature, with the formation of benzoic acid (77MI2).

IV. Heterocycles Retaining the Furanone Ring

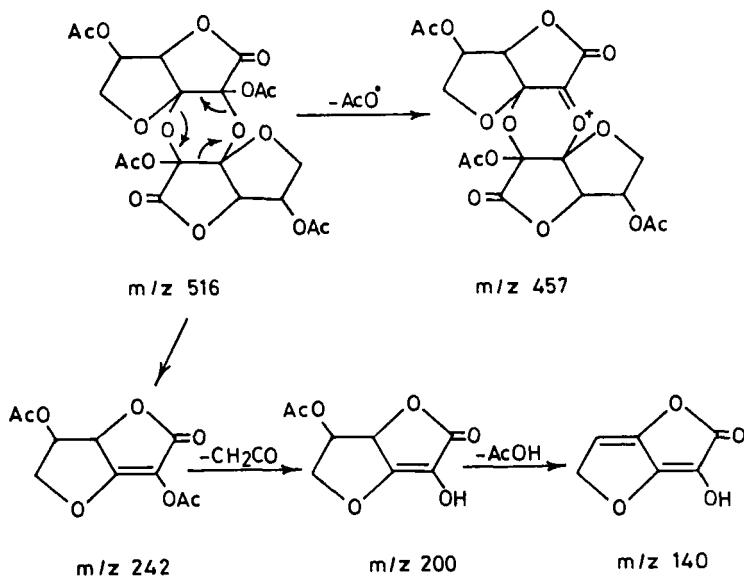
This type of heterocycle retains the furanone (lactone) ring of the parent compound. The heterocycle may be fused to the furanone ring at various positions. Thus, the fusion may be on C-5 and C-4, C-4 and C-3, or C-3 and C-2. Otherwise the heterocycle may be linked to the C-5 of the furanone ring, which was discussed in Section II.

A. FURO-FURANONES

The principal skeleton for this type of compound could be represented by formula **89**, where a perhydrofuran ring is fused to the C-4—C-5 bond of the furanone ring (Scheme 18). The bicyclic form of DHA and its dimeric form are representative of such a ring and are discussed in Section II. Their spectra were studied (70ZPC52, 70ZPC56). The fragmentation pattern of **22** is shown in Scheme 18. Its X-ray analysis (86MI2) reveals only moderate



89

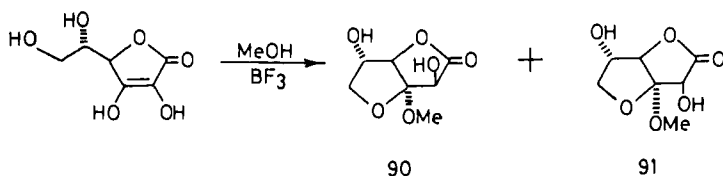


SCHEME 18

deviation from two-fold symmetry, presumably caused by the packing requirements of the acetate groups. The central dioxane ring is stabilized by the conversion of the hydroxyl groups into acyloxy groups.

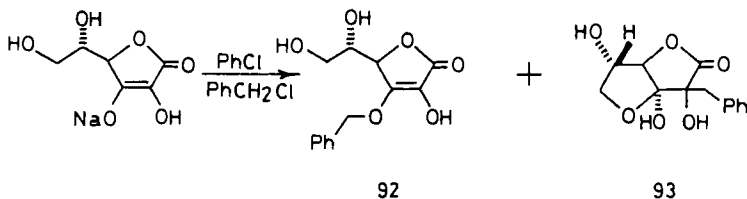
Epimeric lactones **90** and **91** were isolated in low yield from the reaction of **3** with methanol in the presence of boron trifluoride as a catalyst. They have been proposed as intermediates in the acid-catalyzed degradation of **3** to furfural and polymeric materials (77GEP2719303) (Scheme 19).

The monoanion of **3** is an ambident anion that can display nucleophilicity at the C-2 as well as the O-3 positions. Thus, when the alkylation was carried out in water, a mixture of the O-3 and C-2 benzylated derivatives **92** and **93**, respectively, were produced [65CI(L)89, 65CJC450] (Scheme 20). The structure of the methyl glycoside of **93** was confirmed by X-ray crystallography [76AX(B)1665].

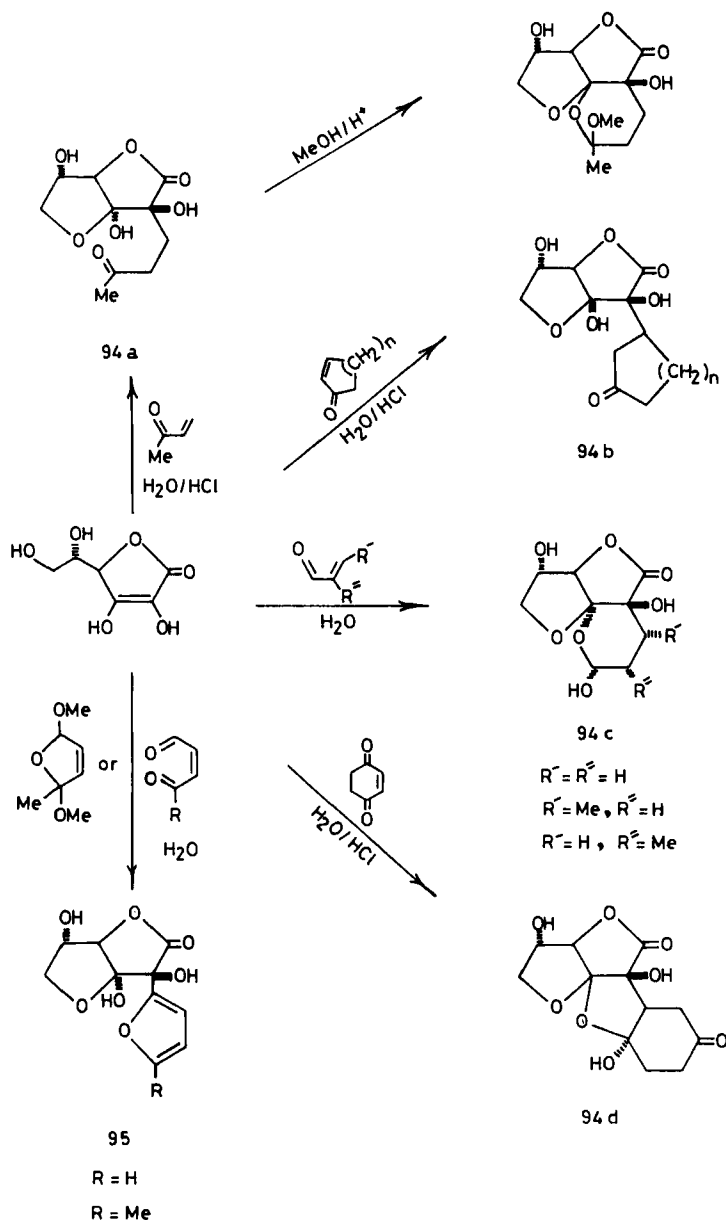


SCHEME 19

Another type of compound having the furo-furanone skeleton, in which a C—C bond was formed at C-2 of **3**, has been achieved by using **3** as a Michael carbanion donor to various α,β -unsaturated carbonyl compounds. Thus, it gives **94a** when combined with methyl vinyl ketone, which can then be converted to the cyclic acetal upon reaction with methyl alcohol in the presence of an acid (83T2137). The reaction was extended to acrolein, α -methyl acrolein, and crotonaldehyde to give **94c**. Its application with 2-cyclohexen-1-one required an unexpected acid catalysis to give **94b**. On the other hand, extending the reaction to a cyclic enedione, 2,3-dihydrobenzoquinone gives rise to 2-(1',4'-diketo-2'-cyclohexyl)-3-keto-L-gulonolactone-3,6-cyclohemiketal which, in turn, is stabilized as the 3,1'-cyclohemiketal **94d** (89H467). 2-Methyl-2,5-dimethoxy-2,5-dihydrofuran, a cyclic acetal of cis-3-acetylacrolein, gave with **3** an amorphous major product of 2-(5-methyl-2-furyl)-3-keto-L-gulonolactone-3,6-hemiketal **95** (84JOC5064). The reaction mechanism most likely involves cis-3-acetylacrolein (i.e., 4-keto-cis-2-pentenal) as an intermediate. Hemiketal **95** was converted with succinic anhydride into a crystalline molecular complex whose X-ray structure determination showed strong hydrogen bonds between the succinic carbonyl oxygens and the C-3 hydroxyls of 2 mol of hemiketal **95**. Succinimide and *N*-methylsuccinimide also gave very stable molecular complexes, while maleic anhydride and *N*-phenylsuccinimide did not form crystalline adducts with **95**. The lactone **95** and its adducts show remarkable immunomodulation and an extremely low toxicity.

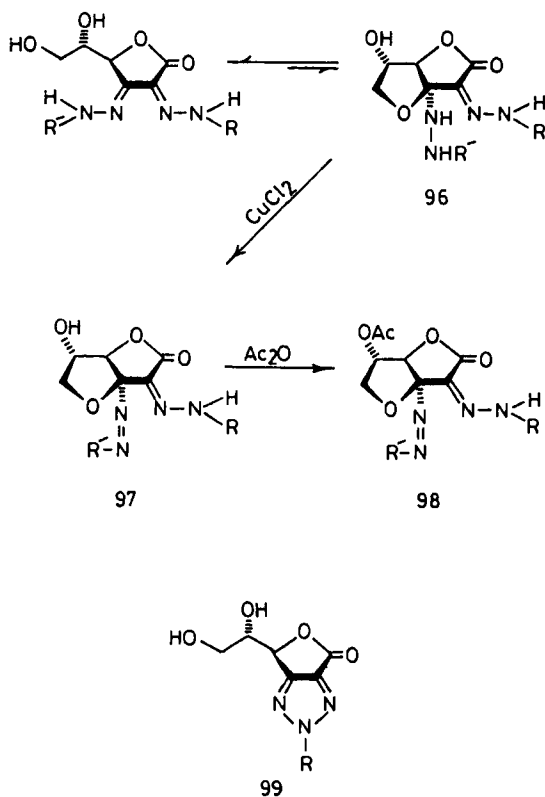


SCHEME 20



SCHEME 21

The nitrogen derivatives of **4** were briefly reviewed (82MI173). When the corresponding bis(arylhydrazones) were subjected to mild oxidants, such as cupric chloride, they gave the yellow bicyclic compound 3,6-anhydro-3-arylazo-2-oxo-L-lyxo-1,4-lactone arylhydrazone (**97**), and not the anticipated triazole **99** (Scheme 22). The structure of **97** was deduced by both degradative and spectroscopic methods [68JCS(C)2251, 68MI2; 73JHC1051]. Its infrared spectrum revealed a lactone band at 1720 cm^{-1} in the same position as that of the starting bishydrazone. Acetylation of **97** afforded **98**, whose $^1\text{H-NMR}$ spectrum showed the presence of only one acetyl group and one imino proton, indicating the loss of one hydroxyl group and one imino proton during the transformation. The uncoupled $^{13}\text{C-NMR}$ spectrum (80JHC1181, 80MI10) of the acetate **98** showed an upfield shift of C-3 (105.0 ppm), compared with that (110.2 ppm) of **65c**, which is consistent with the loss of the double bond at this position. The



SCHEME 22

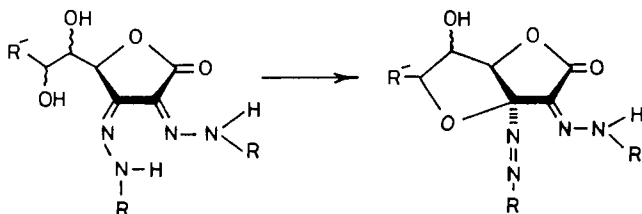
large downfield shift of the resonances of the phenyl carbons (particularly C-1, C-2 and C-4, which appeared at 151.0, 122.5, and 131.5 ppm respectively) instead of the respective carbons in the bishydrazone (which appeared at 143.6, 112.6, and 123.4 ppm, respectively) are incompatible with a benzene ring linked to a hydrazino group, such as structure **96** and agreed with a benzene ring linked to an azo group, as in structure **97**.

The structure of **97** was also confirmed by studying (81MI3) the ^{15}N -NMR spectrum. The proton-decoupled, natural abundance spectrum displayed four signals at 147.5 and 139.8 ppm (characteristic of azo nitrogen nuclei), at -14.2 ppm (for the tertiary nitrogen nucleus), and at -208.5 ppm (characteristic of the secondary nitrogen nucleus). The presence of only one N—H proton was confirmed from the proton-coupled ^{15}N -NMR spectrum, which displayed the three ^{15}N signals at lowest field as singlets, but displayed the signal at the highest field as a doublet ($^1\text{J}^{15}\text{NH}$ 95.2 Hz).

The structure of **97** was put in doubt when electron ionization mass spectroscopy detected a molecular ion peak two units higher than expected (80JHC1181). The mass spectrum of the acetate **98** also showed a molecular ion two mass units more than calculated, which can also be accounted for by the acetate of structure **96**. However, when the mass spectrum of **97** was measured at a lower temperature below the decomposition point of the compound, the expected molecular ion (m/z 394) for structure **97** appeared. Moreover, as the temperature was slowly raised above the melting point, the m/z 396 ion started to appear. This suggests the transformation of the azo compound to **96** or to an isomer on thermal decomposition of the sample.

The UV spectrum of **97** shows an absorption maximum at 365 nm. This is considerably lower than that of the parent bis(hydrazone) **65c**, which appeared at 445 nm. This could be attributed to the disappearance of conjugation with the C-3 hydrazone group in compound **97**.

The oxidation of the bis(phenylhydrazone) described previously was found to be general, whereby other bis(hydrazones) or the mixed bis(hydrazones) could be transformed to the substituted derivatives of **97** (84MI1; 85MI2; 88MI5). On the other hand, the bis(*o*-chlorophenyl) analogue gave the corresponding *o*-chlorophenyl derivative of **97** when subjected to the same condition, without loss of the chlorine atoms (76MI4) as anticipated from the studies in osazone chemistry (61JCS2957; 73MI1). It was assumed that the ortho chlorine atom and the hydrazone residue form a complex that facilitates the removal of the ortho halogen. Such a complex explains why the meta and para substituents do not undergo such a reaction. The only halogen in the ortho position that is retained in the molecule under these conditions is the fluorine atom. This was attributed to the fluorine



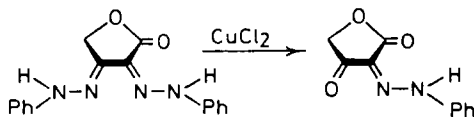
SCHEME 23

being more strongly bound than the other halogen atoms. The retention of the ortho chlorine in the above reaction may be attributed to the facile susceptibility and consequently the mild condition of the oxidation of the hydrazo group to the azo group. The oxidation could be achieved by various oxidizing agents such as nitrous acid and iodine. This facile loss of the two hydrogen atoms may be due to the presence of the bis(hydrazono) **65c** in equilibrium with a bicyclic hydrazo form **96**.

The oxidation just discussed was successful with analogues possessing longer side chains (70MI4; 72MI2) or other configurations (Scheme 23). On the other hand, when the 2,3-bis(phenylhydrazono) of the four-carbon analogue with no side chain was treated with cupric chloride as previously described, partial hydrolysis occurred and the phenylhydrazono **52** was obtained (76MI2) (Scheme 24). Reduction of **60** with sodium borohydride gave the corresponding alcohol, whose acetylation gave the 3,6-anhydro derivative (82MI2).

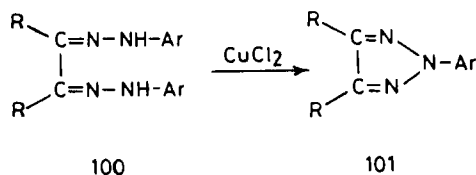
B. FURO-TRIAZOLES

A general method for synthesizing triazoles **101** from bis(arylhya-zones) **100** was achieved by various oxidizing agents, such as metal salts in their higher valency state, nitrous acid, and halogens such as bromine (Scheme 25). The latter bromination affords the corresponding *p*-bromophenyl derivative of **101**. These reactions are applicable with various



52

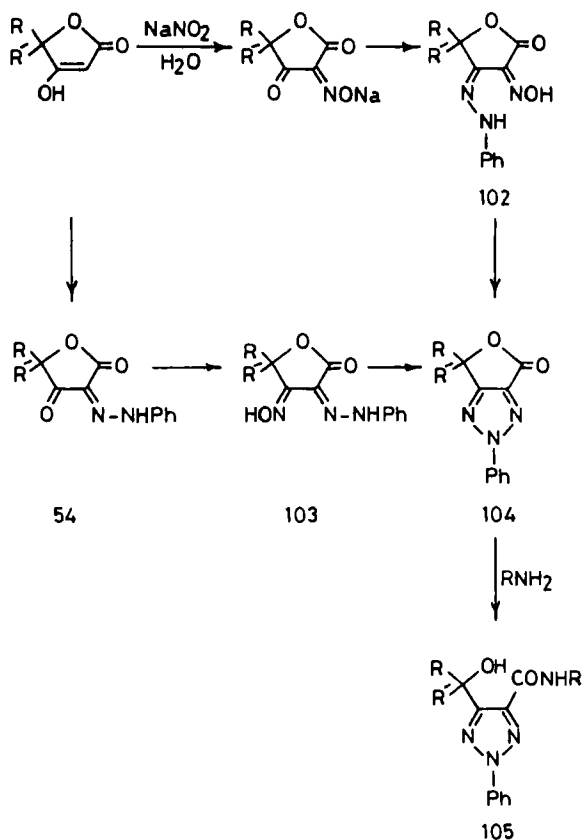
SCHEME 24



SCHEME 25

substituents on the two sites of diketone bis(arylhydrazones). However, when the two carbonyl groups are a part of a furantrione ring, the reaction proceeds differently, and no triazole derivatives are isolated.

Pollet and Gelin (79S977) elaborated a convenient synthesis for the fused [furo-3,4-*d*]triazoles **104** bearing a furanone ring suitable for further transformation to 4-(1-hydroxy-alkyl)-2*H*-vic-triazole **105** (Scheme 26).

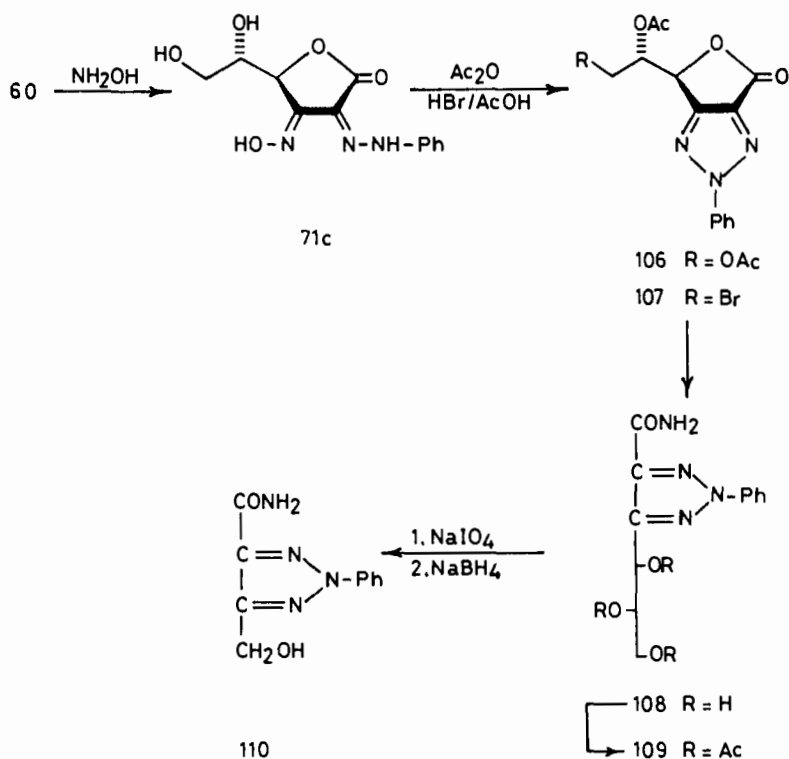


SCHEME 26

Two routes have been examined. Sequential coupling of the tetronic acid analogues with benzene diazonium sulfate gave **54** [1896AC(R)244; 1900AC(R)155]; oximation with hydroxylamine hydrochloride and sodium acetate gave **103**; and cyclodehydration of **103** in acetic anhydride afforded the [3,4-*d*]triazoles **104**. More conveniently, the three-step elaboration of **104** was done by treating the tetronic acid with sodium nitrite and then phenylhydrazine hydrochloride to give **102** via the formation of the sodium salt of the oxime. Cyclodehydration of **102** gave **104**.

A better cyclodehydrating process was performed by phosphorus pentachloride in dimethoxyethane at room temperature. The synthetic potentiality of the furanone ring of **104** in the synthesis of functionalized 1,2,3-triazoles by the cleavage with ammonia and amines has been explored.

Sequential conversion of DHA into the hydrazone **60**, followed by oximation gave the oxime **71c** (77ACH409; 88MI4), then cyclodehydration gave 4-*L*-threo-2,3-di-acetoxy-(1-hydroxypropyl)-2-phenyl-1,2,3-triazole-5-carboxylic acid 1,4-lactone **106** (77MI3) (Scheme 27). The infrared spec-



SCHEME 27

trum of **106** showed a lactone carbonyl band at 1800 cm^{-1} shifted to a higher value than that of its precursor because of the absence of hydrogen bonding. The $^1\text{H-NMR}$ spectrum of **106** showed signals agreeing with the structure. Its mass spectrum showed a molecular ion peak and a base peak that due to the loss of the diacetoxylethyl side chain from **106**. Compounds of this type could be precursors for other triazole derivatives. Thus, upon treatment of **106** with liquid ammonia, deacetylation occurred to give **108**. Acetylation of **108** gave **109**, whereas its periodate oxidation followed by borohydride reduction afforded **110**. The reaction of **71c** with hydrogen bromide in acetic acid afforded **107**. The reaction was achieved using hydrazones possessing different substituents on the hydrazone residues and on the *D-erythro* analogue to afford triazoles with a variety of substituents (79MI1; 82MI3; 82MI8).

C. FURO-DIAZINES

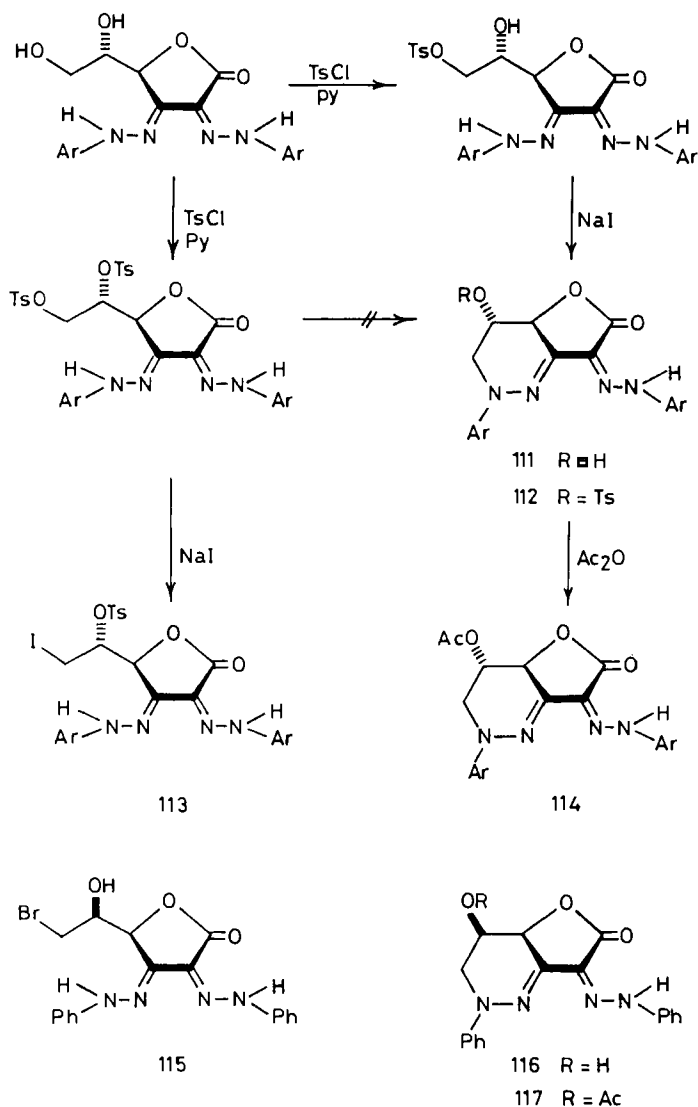
The synthesis of this type of compound was achieved by nucleophilic attack of the nitrogen of the C-3 hydrazone residue on C-6 of **65c** when it carries a leaving substituent such as a sulfonyloxy group or a bromine atom. This intramolecular heterocyclization process was achieved by the action of sodium iodide in acetone or by the action of acetic anhydride on the mono-*O-p*-toluene sulfonate to give **111** and **114**, respectively (82MI5) (Scheme 28). The spectral data confirmed the assigned structure.

When the di-*O-p*-toluene sulfonyl derivative was subjected to the action of sodium iodide in acetone under the previous condition, a product **113** was obtained as a result of the nucleophilic displacement of the primary tosyloxy group by the iodide ion. This is probably due to the steric effect of the tosyl group on position 5.

The *D-erythro*-analogue **116** was obtained from the reaction of 6-bromo-6-deoxy-dehydro-*D*-isoascorbic acid with phenylhydrazine (80MI5). The reaction had probably taken place via the formation of the corresponding bis(hydrazone) **115**, followed by nucleophilic displacement of the bromine atom by the participation of the hydrazone residue to give **116**, whose acetylation gave **117**. Reaction of the 2,3-diamino analogue **118** with dicarbonyl compounds gave the diazine **121** (37CB1862; 82MI6).

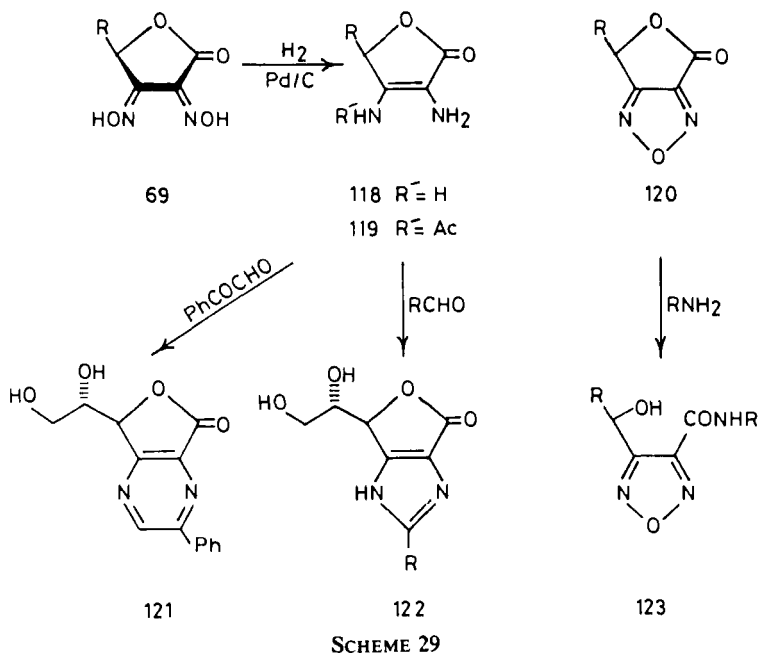
D. FURO-IMIDAZOLES

The 3,4-diamino-(5*H*)-2-furanones are considered ideal starting materials for synthesizing various heterocyclic compounds. An efficient synthe-



SCHEME 28

sis is the catalytic hydrogenation of the corresponding dioxime to give **118** (79S977; 82M11) (Scheme 29). The hydrogenation of the dioxime instead of the corresponding bis-(phenylhydrazone) avoids the tedious separation of the enediamine from the aniline product. Reaction of **118** with different aldehydes gave the furo[3,4-*b*]imidazoles **122** (37CB1862; 74M12),



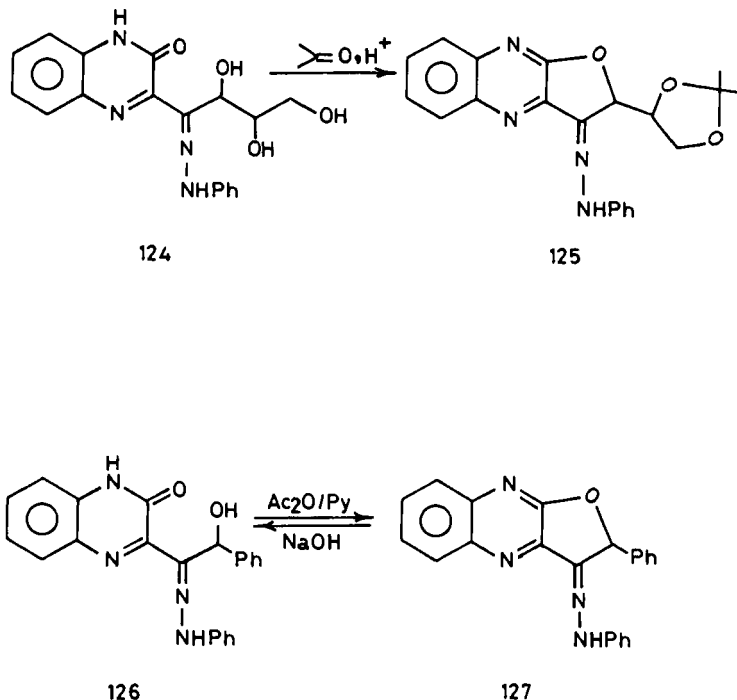
whereas the acetylation gave **119**. Attempted reduction of the diamines, with the aim of using them in the synthesis of biotin model compounds, was only successful after acylation (46M11).

E. FURO-FURAZANS

Cyclodehydration of the dioxime with thionyl chloride in dioxane gave 4-oxo-4,6-dihydrofuro[3,4-*c*]furazans **120** (79S977). Opening of the lactone ring with amines led to functionalized 1,2,5-oxadiazoles **123**.

F. FURO-QUINOXALINES

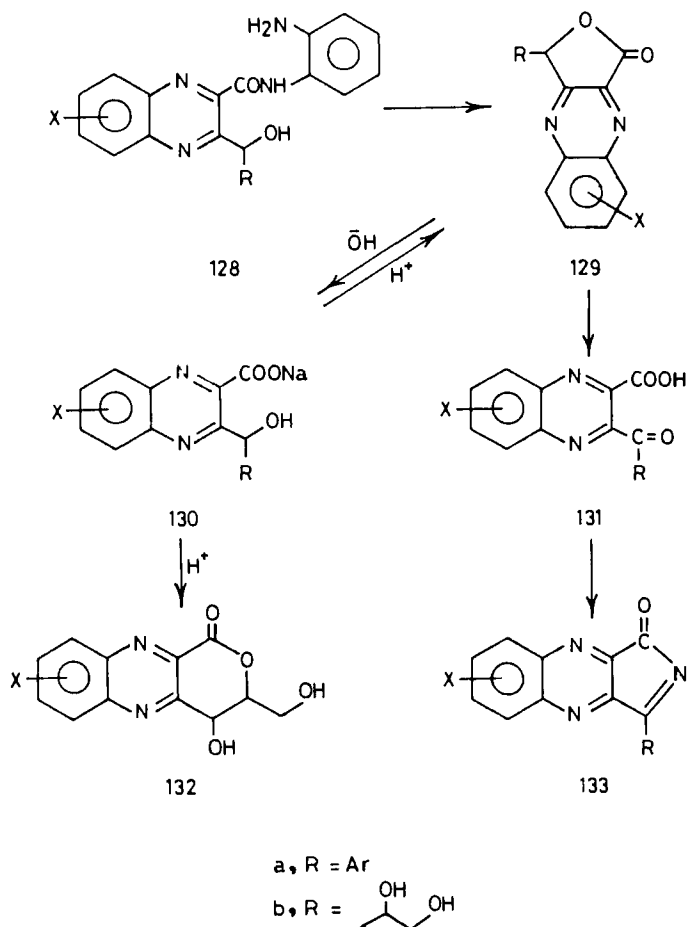
These compounds are divided into two main types. The first has the quinoxaline ring fused to the 2 and 3 positions of the furanone ring, whereas the other type has that ring fused to the 3 and 4 positions. These compounds were prepared from quinoxalinones or quinoxalines obtained from the reaction of furantriones with one or two molar equivalents of *o*-diamines



SCHEME 30

(see Section V). Two methods can be used to form the first type. In compounds containing a triol residue, such as **124**, dehydrative cyclization takes place under isopropylidenation to give **125** (unpublished results) (Scheme 30). A similar reaction takes place on the *D-erythro* isomer. Although another type of dehydrative cyclization takes place under acylation of **124** (see Section V), analogue **126** gave **127** on acetylation and benzoylation [90JCS(P1)2513]. Reaction of **127** with alkali opened the ring to give **126**.

Compounds of type **129** were prepared by the action of hydrochloric acid on **128**, which was prepared from the respective furantrione (Section V,G) (54HCA1318; 64HCA1860; 66HCA2426; 86MI5) (Scheme 31). The quinoxaline **129b** gave a diacetyl and an isopropylidene derivative. Treatment with sodium hydroxide caused the opening of the lactone ring and formation of the sodium salt **130**, which, on acidification, gave a mixture of lactones **129** and **132**. Compounds with various substituents on the aromatic ring and on the dihydroxyethyl residue as well as derivatives from the opening of the lactone ring were prepared (84MI2; 86MI9). Oxidation

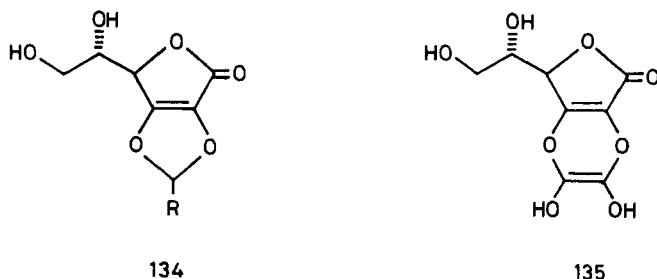


SCHEME 31

of **129a** followed by oximation gave the condensed isoxazole **133a** (66HCA2426).

G. FURO-DIOXOLANES AND DIOXANES

As a consequence of Albert Szent-Györgyi's (76MI1) bioelectronic theory of cancer, L-ascorbic acid was used as a carrier for methylglyoxal and its derivatives. Therefore, the reaction between such carbonyl compounds and **3** attracted the attention of Fodor and others (79MI3; 80MI1). Thus,



SCHEME 32

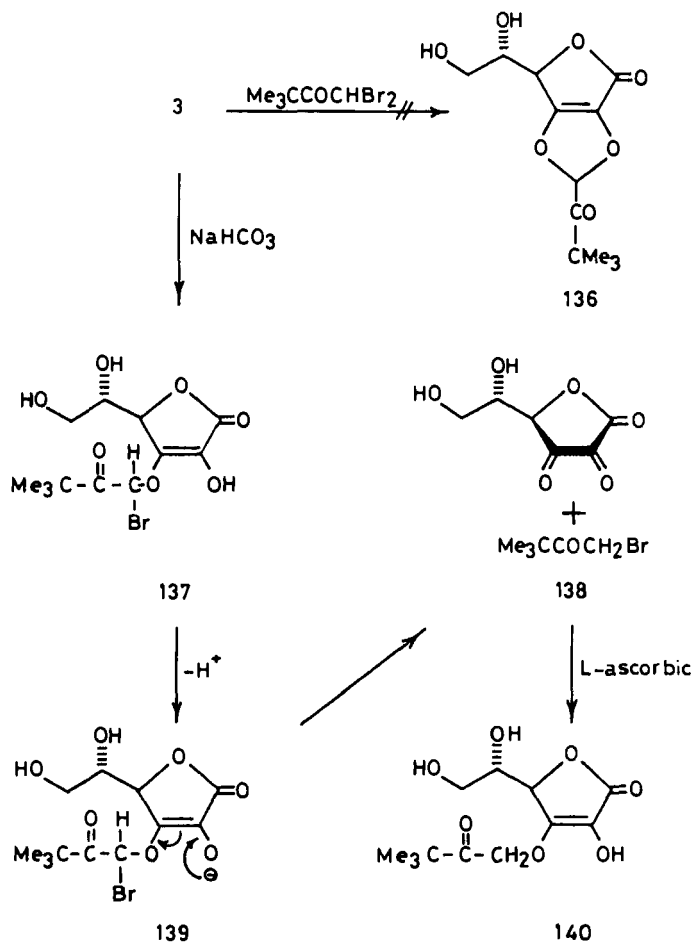
3 gives new acetals **134** with α -ketoaldehydes. The 2,3-dioxole ring was formed from the reactive aldehydes under kinetic conditions; glyoxal is reported to afford the novel enediol bisacetal **135** (76USP3888989). These data open the possibility of direct oxidative modification of the ascorbic acid side-chain (Scheme 32).

An attempt to prepare the dioxole **136** by treating **3** with a suitable *gem*-dibromide, such as 1,1-dibromopinacolone, was reported (82MI4). However, the product was the open chain 3-*O*-(3,3-dimethyl-2-oxobutyl) ascorbate **140** and not the dioxole **136** (Scheme 33). On the other hand, an intermediate **137** containing one bromine atom as well as DHA could be trapped. Consequently, the proposed mechanism involves alkylation of **3** to **137**, intramolecular redox reaction to **138** and DHA via **139**, and finally alkylation to give **140**. Note that this type of ring system was previously reported (61JA3504).

5,6-Dihydroxy-*N*-methylindole **142** readily reacts with DHA in aqueous solution at room temperature (64CJC1401; 65JCS4728) (Scheme 34). The two hydroxy groups of the indole interact with the α -diketone function of DHA to form the 1,4-benzodioxane **144**. This type of reaction appears to be general since similar interactions occur between other *o*-diphenols and α -diketones. The mechanism by which the 1,4-benzodioxane derivative is obtained when adrenochrome **141** is reduced with ascorbic acid to give **142** via **143** was studied.

The reactions of either 3-hydroxymethylindole with **3** or of indole, formaldehyde, and **3** gave ascorbigen (57CCC654, 57CLY1197, 61MI1; 62ACS1286), which is a bound form of **3** that has been isolated from cabbage and other sources.

On the other hand, the formation of dioxolane linked to the furantriones of general structure **146** is straight-forward and readily obtained by the oxidation of **145** [32N(L)847; 68MI4; 72BBA207; 75ANY48] (Scheme 35). It has been studied more extensively than the 2,3-acetals previously men-

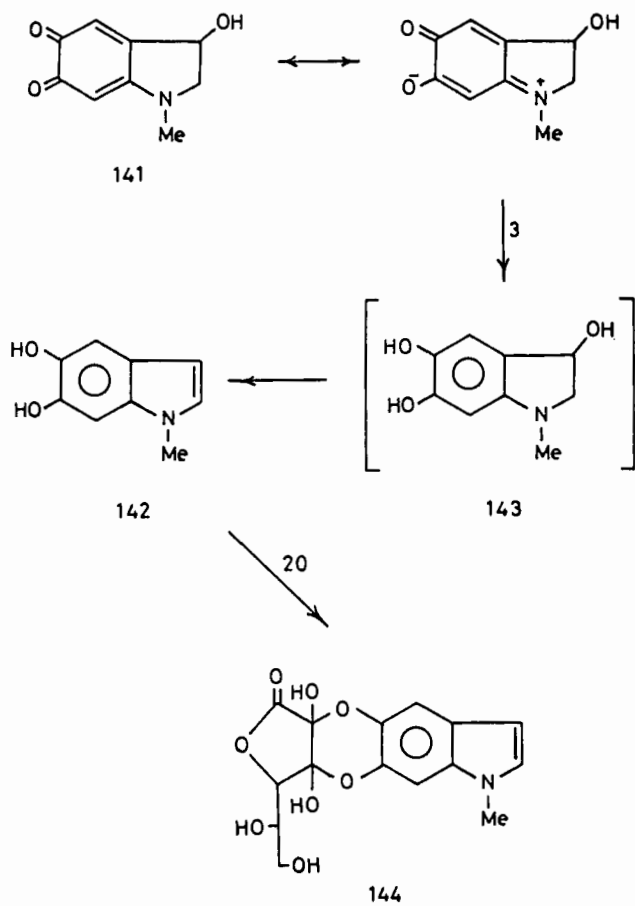


SCHEME 33

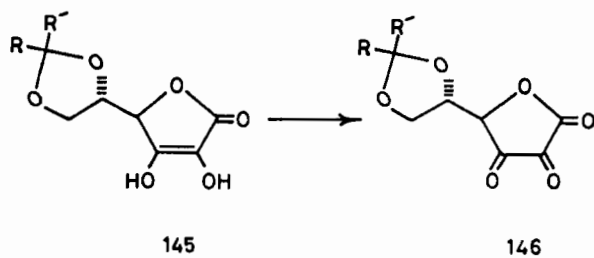
tioned. Their significance is not only for their use as protecting groups, but also for their commercial importance as lipophilicity modifiers for **3**.

H. LACTONES AND SPIRODILACTONES

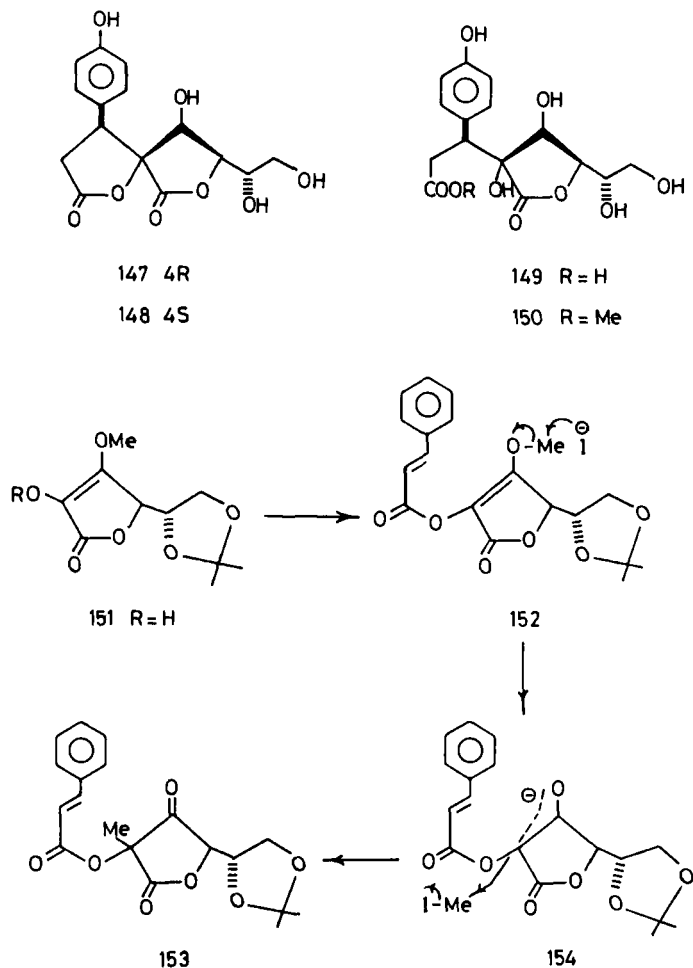
Part of the skeleton of some natural products resembles that of **3**. Leucodrin **147** [1896LA(290)314] and conocarpin **148** [70JCS(C)2127] have been isolated from the leaves of *Leucadendron* species and *Leucospermum*



SCHEME 34



SCHEME 35



SCHEME 36

refluxum, respectively (Scheme 36). Conocarpic acid **149** and reflexin **150** were also obtained (72JCS2450, 72JCS2457). The realization that their B-ring bears a resemblance to **3** led to a study of the reaction between alkyl 3-bromo-3-phenylpropionate and L-ascorbic anion (75M11). However, the reaction did not yield C- or O-substituted derivatives of **3**. Instead, the corresponding (*E*)-cinnamates of 3-hydroxypropionic acid were obtained, depending on whether alkaline or acidic conditions were used. Successive unimolecular methylation to give **151** and (*E*)-cinnamoylation of 5,6-*O*-

isopropylidene-L-ascorbic acid furnished 2-*O*-(*E*)-cinnamoyl-5,6-*O*-isopropylidene-3-*O*-methyl-L-ascorbic acid **152**, which was transformed into the isomeric 2-*C*-methyl derivative **153** via **154**.

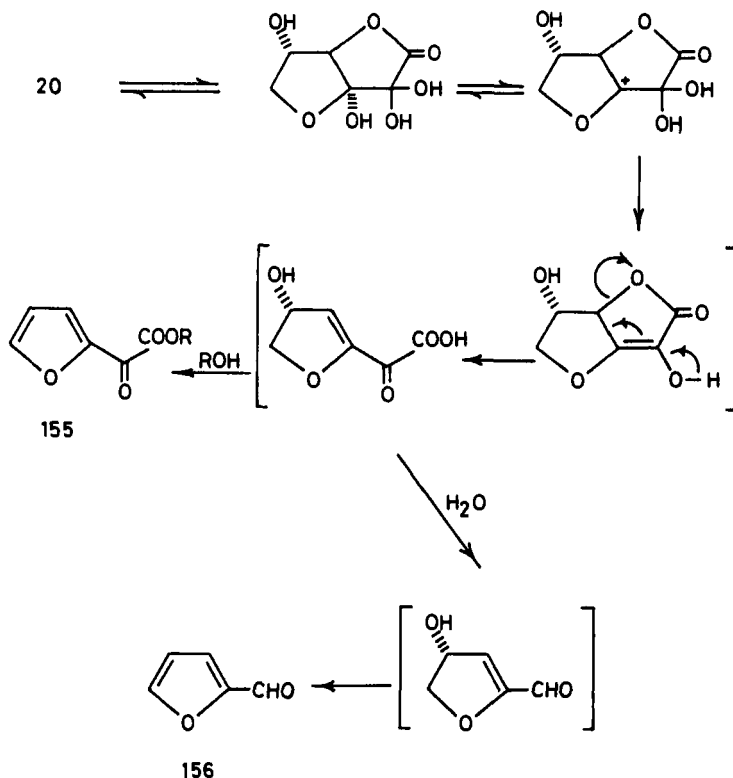
I. MISCELLANEOUS

DHA gave a blue color with pyrrole, 3,4-dimethylpyrrole, and 2,2'-bipyrrole (69MI1; 70MI2). On the other hand, pyrrole having substituents at the 2- or 2,5-positions, or other five-membered heterocycles such as furan, thiophene, or pyrrolidene, failed to give such a blue color when they were substituted for pyrrole. Although other attempts to isolate the reaction product failed, the use of the 6-benzoyl derivative of DHA instead of DHA did allow isolation. Based on IR spectroscopy and elemental analysis, it was concluded that the blue compound possesses an indophenine structure.

V. Heterocycles from Rearrangement of the Furanone Ring

A. FURAN DERIVATIVES

Extensive studies have been reported on the products of degradation of **3** under a variety of reaction conditions [34HCA311; 44MI1; 59BSF74; 60NKZ13; 63JPS948; 65JPS124, 65JPS181, 65YZ42; 66JA246; 67ABC170, 67ABC177; 71TL2503; 72BCJ3692, 72JOC(37)1606; 73BCJ902; 86MI7; 87MI2; 90MI4]. Both **3** and DHA are unstable in solution and undergo a variety of further degradation reactions involving fragmentation to lower molecular weight compounds and further dehydration to other reactive intermediates. In acidic media, **3** dehydrates to give 2-furfuraldehyde and carbon dioxide. In addition to furfuraldehyde, ethyl glyoxal, 2-keto-2-deoxy-L-pentono- γ -lactone and L-xylosone could be isolated as their mono- and bis-2,4-dinitrophenylhydrazones from the degradation of DHA. Among the large number of degradation products produced, threonic, oxalic, glyceric, glyoxalic acids, and threose were also identified by gas-liquid chromatography-mass spectrometry (GLC-MS). From the kinetic point of view, it has been concluded that the degradation does not proceed via L-xylo-2-hexulosonic acid as an intermediate; but no experimental proof on that proposed pathway has been provided. On the other hand, another pathway was proposed based on the isolation of 3-deoxy-L-2-pentosulose. The degradation of **3** in methanol gives 2-methoxalylfuran **155**, but degradation in water yields **156** (Scheme 37).

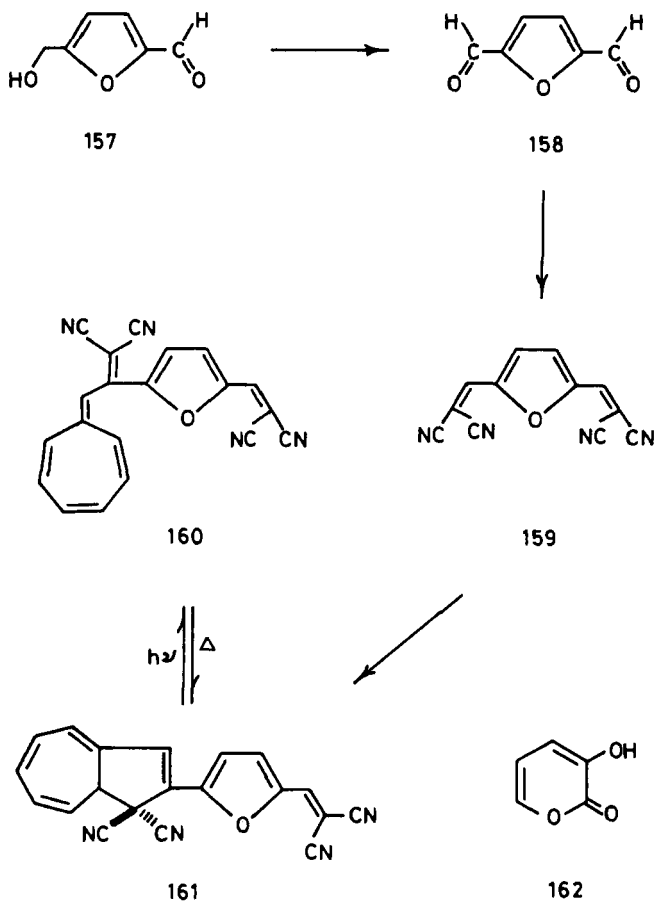


SCHEME 37

The furfural derivative **157** that is commercially available from the degradation of carbohydrate is an excellent precursor for other heterocycles of potential application (Scheme 38). Thus, the tetracyano derivatives **159** derived from **158** have technically interesting properties, such as electrical conductivity and electron storage. A two-step reaction of **159** with 8-methoxyfulvene gave the photochromic **161**, whose rearrangement by irradiation with visible light gave the thermo-chromic **160**, which gave **161** under thermal conditions. Thus, such reaction pathways offer opportunities for converting carbohydrates as renewable resources to material devices (85CB1836; 86CB2631; 87MI3, 87MI4; 88MI7, 88MI8).

B. PYRONE DERIVATIVES

3-Hydroxy-2-pyrone **162** was isolated (76ABC1287) from the ether extract of the heated DHA solution as a main aroma compound produced

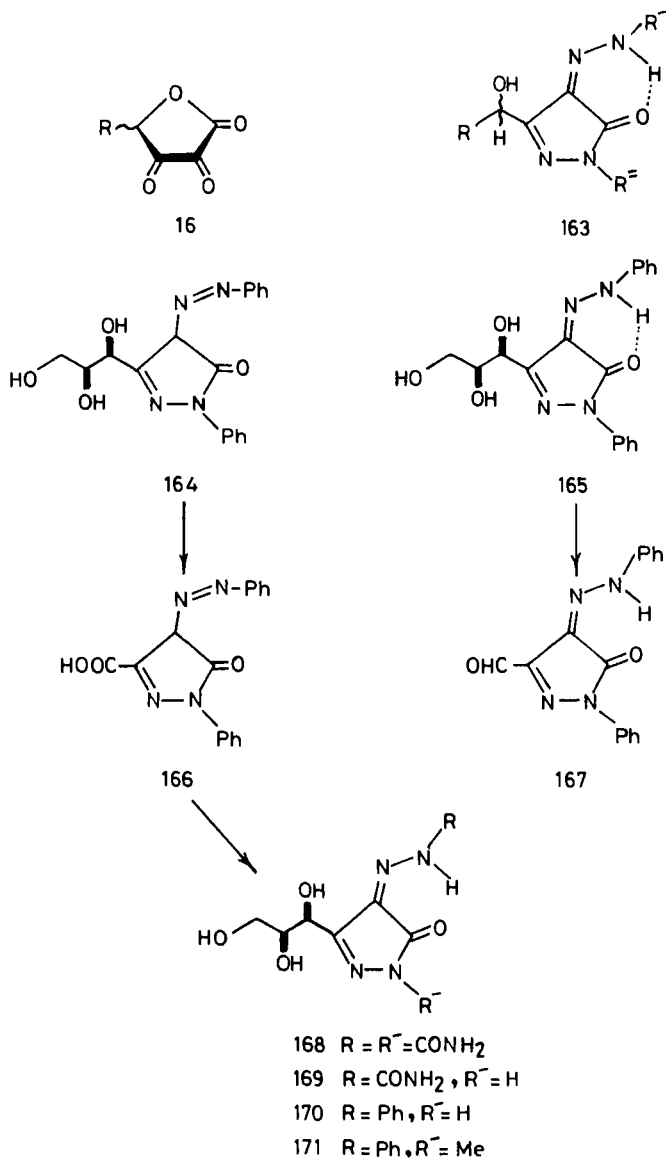


SCHEME 38

from DHA. It was also detected in the reaction of DHA with methionine (79MI4). 3-Keto-4-deoxypentosone was also isolated from the reaction and was considered one of the possible intermediates in the browning reaction.

C. PYRAZOLINEDIONES

Ring-opening of the bis(arylhydrazones) of the furantriones **16** provides access to pyrazolinediones **163** via cyclization of the resulting carboxyl group with the 4-hydrazone group in base (80MI3) (Scheme 39). The rearrangement product of **65** in alkali when acidified was formulated by

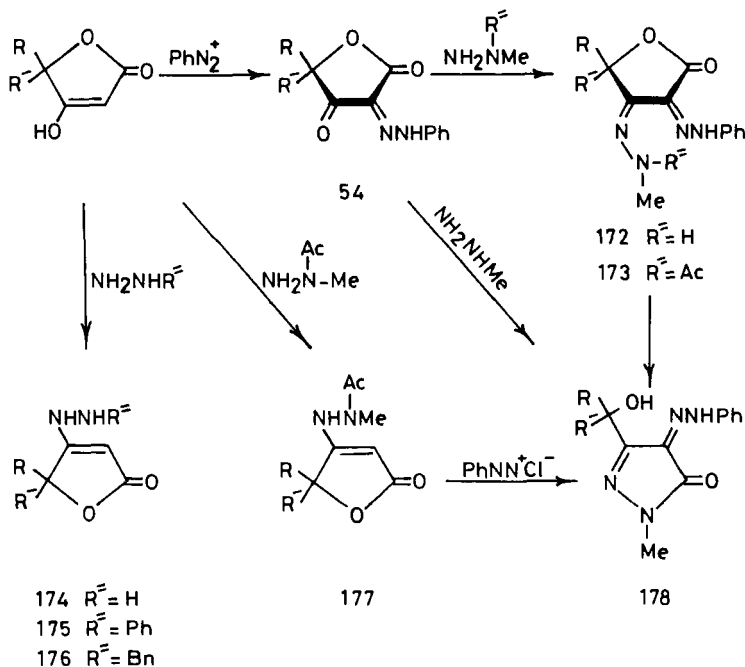


SCHEME 39

Ohle (34CB1750) as the azo pyrazolinone **164**. This was established by oxidizing it to 3-carboxyphenyl-4-phenylazopyrazolin-5-one **166**. Later, on the basis of ^1H -NMR data (72M12), the structure was formulated as the hydrazone **165**. The reaction could be extended to compounds with various

substituents on the aryl residues [68JCS(C)2248; 76CI(L)372; 77MI1]. The bis(semicarbazone) **67** gave **168** and **169** upon dissolution in liquid ammonia and acidification with dilute sulfuric acid (64CR587; 66BSF522). Similar treatment of a mixed phenylhydrazone semicarbazone gave **170** (83MI3). Moreover, the availability of the mixed bis(hydrazones) provides access to compounds having various substituents on the pyrazoline ring (77MI4; 78MI6).

Coupling a tetronic acid with benzenediazonium sulfate (55RTC1217) gave **54**, whose reaction with acetylmethyl-hydrazine and subsequent alkaline treatment gave **178** via **173** and **172** in poor yield (Scheme 40). On the other hand, reaction of **54** with methylhydrazine directly gives **178** in high yield (81MI1). When the reverse order of introduction of the two hydrazine moieties on the tetronic acids was tried, the same pyrazolinedione was obtained. Thus, the reaction with various hydrazines gave **174–177** (79JHC505). Treatment of **177** with alkali followed by the diazonium salt gave **178**. Unexpectedly, reaction of **60** with methylhydrazine gave **171** without isolation of the intermediate bis(hydrazone) [76CI(L)372, 76MI3], and the reaction could be extended to other aryl hydrazones and to the *D-erythro* analogue (78MI6; 81MI7).



SCHEME 40

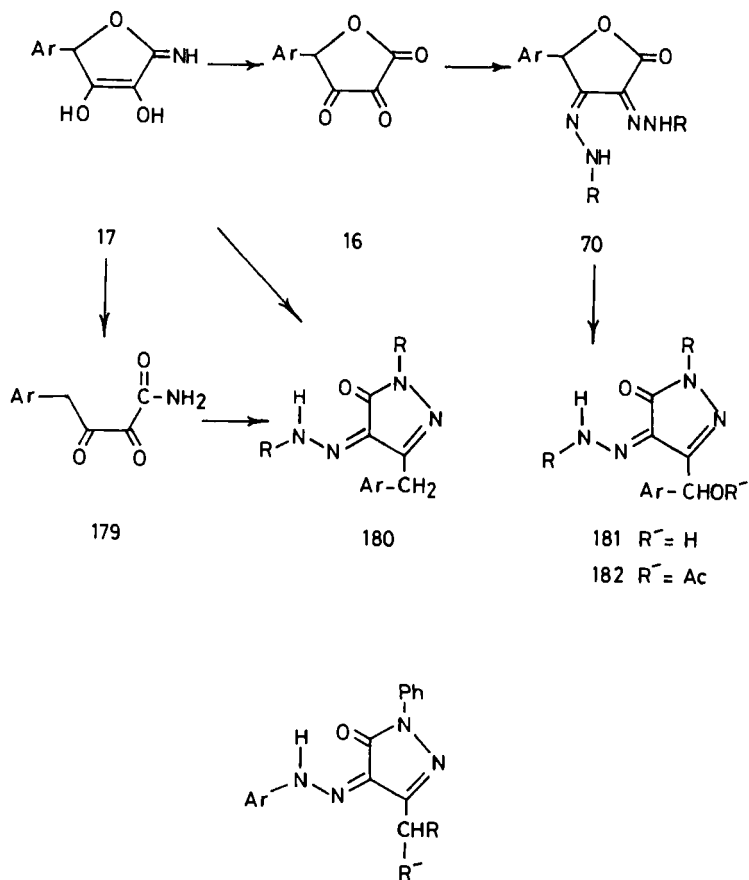
Another way of introducing substituents on the ring is by varying substituents on C-5 of the furantrione ring. In this way, compounds having various substituents on C-5 have been prepared (78MI4; 81MI7). Thus, analogues of **163** having a 1,2-dihydroxyethyl group or a 1,2,3-trihydroxypropyl group or one of these groups without a side chain afforded the corresponding analogues of **164** bearing substituents having the D-arabino- and L-xylo-tetrahydroxybutyl or hydroxymethyl side chains, respectively. Acylation of the compounds afforded the corresponding per-*O*-acylated derivatives (76MI3; 77MI1; 77MI4, 78MI4; 80MI3; 81MI7; 85MI2; 86MI10).

The infrared spectra of the pyrazolinediones showed a characteristic band at 1660 cm^{-1} assigned to the carbonylamide group. The $^1\text{H-NMR}$ spectra of the acylated derivatives were studied frequently and usually showed the presence of an NH signal at ~ 13 ppm, agreeing with the hydrazono structure and suggesting the involvement of the NH in hydrogen bonding. The coupling constants of the protons on the side chains allowed conformations to be assigned (88G687). Those having a D- or L-*threo* configuration prefer the sickle conformation. However, the proportion of the sickle conformation is less than that of the extended zig-zag conformation in those having the D-*erythro* configuration. The D-*arabino* compound adopts an extended planar zig-zag arrangement.

The mass spectrum of some pyrazolinediones showed the molecular ion peak as the base peak. This was followed by three main series of ions that could be characterized according to the number of carbon atoms of the sugar moiety present in the fragment. A possible fragmentation pattern has been reported (77MI1).

The reaction of the tetronimide **17** with boiling 40% acetic acid gave **179**, whose treatment with arylhydrazines gave deoxy pyrazolinedione **180** (54HCA1309, 54HCA1318; 60HCA1555) (Scheme 41). On the other hand, the bis(hydrazone) **70** rearranged with alkali to give the pyrazolinedione **181** (77MI2). The latter afforded a monoacetyl derivative **182**, confirming the presence of one hydroxyl group that resulted from the opening of the lactone ring. This led to two conclusions: the rearrangement occurred in a manner similar to that of other analogues, and no deoxygenation process occurred during the opening of the furanone ring of **70**. The reaction of **179** probably proceeds by the nucleophilic attack of the nitrogen lone pair of electrons on the carbonyl group followed by loss of ammonia. Similarly a number of the pyrazolinediones linked to other nitrogen heterocyclic compounds of the general structures **183** and **184** could be prepared by the same methods used for the aryl analogues.

Another way of varying substituents on the ring was done by reactions on the preformed pyrazolones. Thus, reaction of **165** with hydrogen bro-



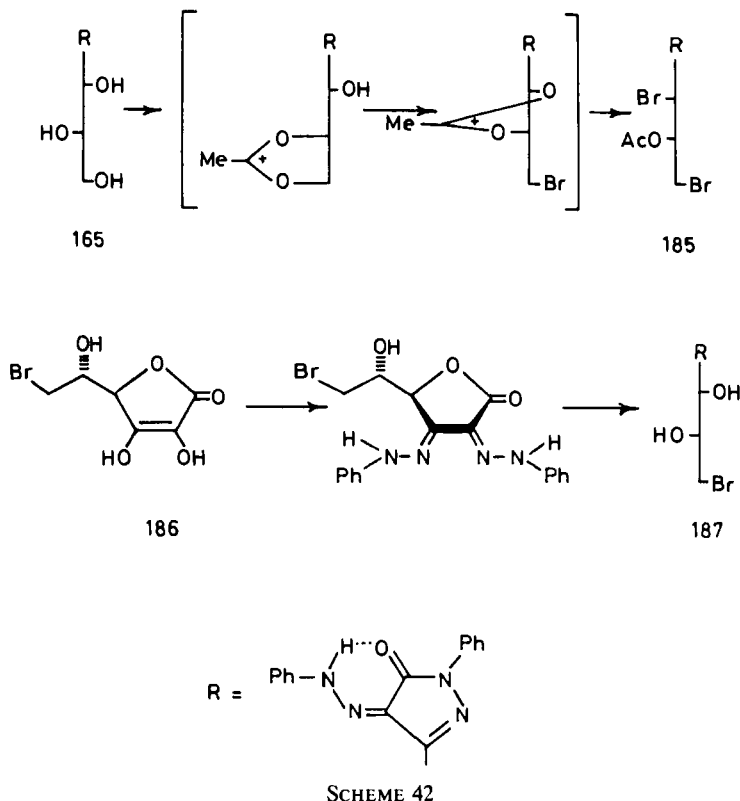
R⁻ = heterocycle

183 R = H

184 $R = OH$

SCHEME 41

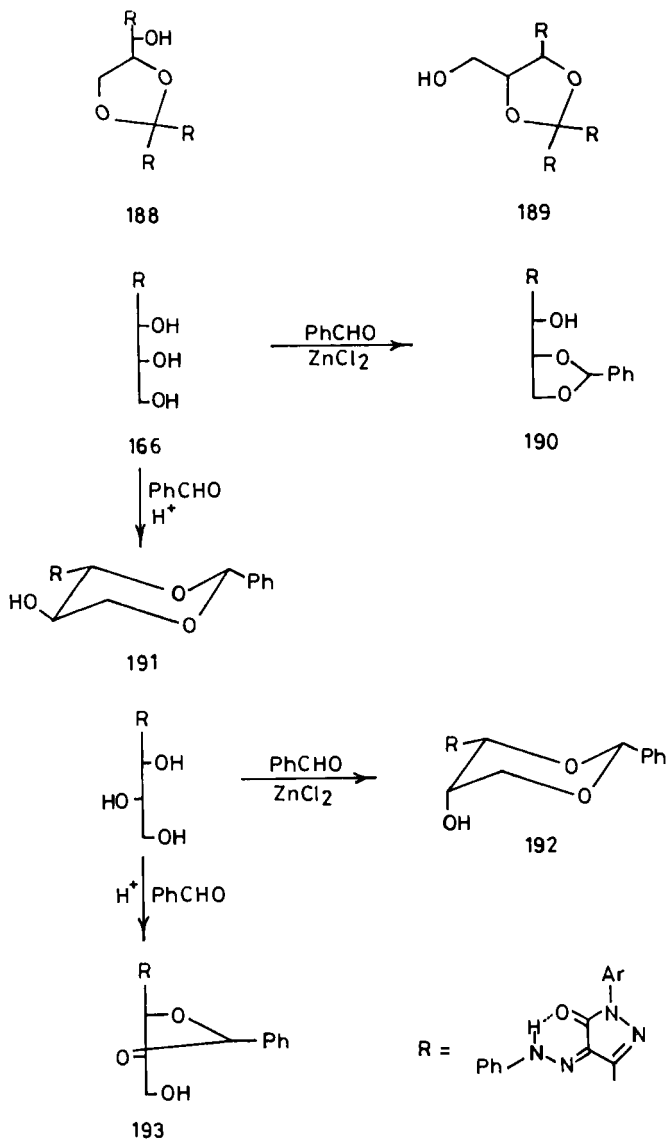
mide in acetic acid afforded a product whose structure was confirmed to be **185** (80MI4) (Scheme 42). The introduction of the bromine into the vicinal diols of **165**, using HBr–AcOH, occurred via a 1,3-dioxolan-2-ylum ion intermediate to give a *trans*-bromoacetate. The inversion of the configuration of C-1 was confirmed by X-ray crystallographic analysis of **185** (unpublished results). The 3-bromodeoxy derivative **187** was isolated during the reaction of phenyl-hydrazine with **186** (78PAC1385; 79MI2). The formation of such a product can be explained as a consequence of the



rearrangement of the corresponding bis(hydrazone) by the basic nature of phenylhydrazine. The pyrazoline was found to be a byproduct during the formation of the bis(hydrazone).

1. *Pyrazolinediones Linked to Dioxolanes and Dioxanes*

This type of compound was prepared by the reactions of ketones [83MI4; 86CC1024, 86MI6; 87MI1, 87MI5; 88JCS(P1)133, 88MI1, 88MI2, 88MI3] or aldehydes [86MI1, 86MI3; 88JCS(P1)139] with the glycerol residues of **165**. Under kinetically controlled conditions, the dioxolanes of type **188** were obtained from the reaction of ketones with glycerol residues having any configuration, whereas **189** was obtained under thermodynamically controlled conditions via the rearrangement of those having a *threo* configuration (Scheme 43). The *erythro* isomer could not be rearranged. The dioxolane **190** was prepared by the reaction of the *D-erythro* analogue with



SCHEME 43

PhCHO—ZnCl₂, whereas its reaction with PhCHO—H⁺ gave the dioxane **191**. On the other hand, the *threo*-analogue of **165** gave, under zinc chloride catalysis, the corresponding dioxane **192**, whereas under acid catalysis, it gave dioxolane **193**.

3. *Rubiazonic Acid*

Reduction of **165** with Zn/AcOH in ethanolic solution afforded substituted rubiazonic acid **200**, whose structure was confirmed by IR and ¹H-NMR spectra [72JOC(22)3523].

D. ISOXAZOLINEDIONES

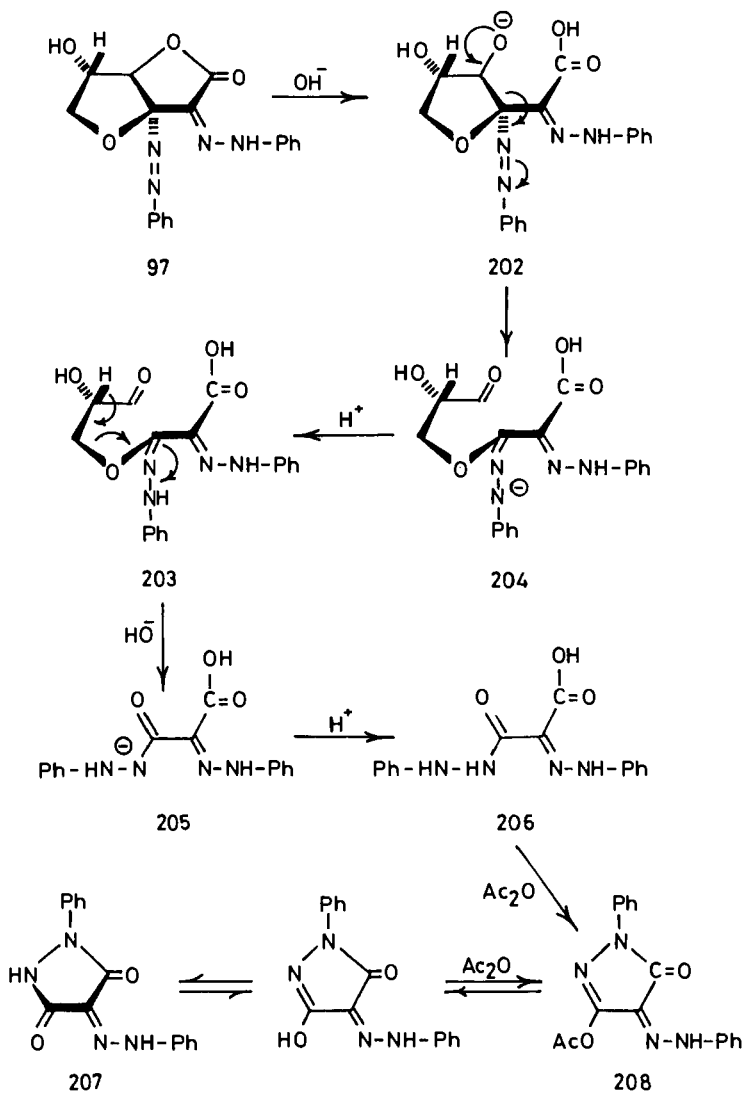
On controlled treatment of the hydrazone oxime (**71c**) with sodium hydroxide followed by acidification, the isoxazolidione **201** was obtained (82MI8; 83MI5).

E. PYRAZOLIDINONES

Treatment of **97** with alkali followed by acidification gave mesoxalic acid phenylhydrazone monophenylhydrazide **206**, whose structure was deduced from studying its ¹H-NMR and mass spectra (73JHC1051) (Scheme 45). Its formation can take place by opening of the lactone ring to give **202** under the influence of alkali, followed by a reverse aldol reaction to give intermediate **204** having an aldehydic group. This then underwent β -elimination to give **205** via **203**, which upon protonation gave **206**. Its acetylation yielded 3-acetoxy-1-phenylpyrazoline-4,5-dione-4-phenylhydrazone **208**, whose deacetylation gave the pyrazolidinone **207**.

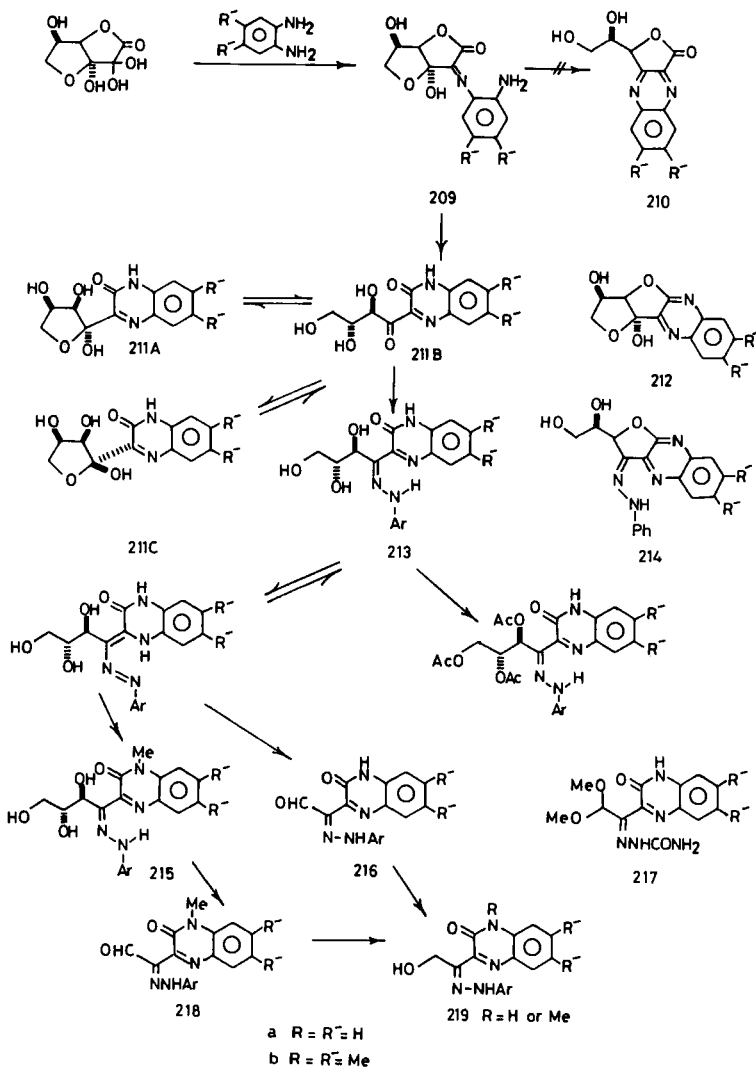
F. QUINOXALINONES

The reaction of DHA and its *D-erythro* analogue (DHI) with *o*-phenylenediamine gives a variety of products, depending on the molecular proportions of the reactants (34CB555; 35CB2262; 52AK369; 53JPJ309; 54HCA1318; 57AG479; 59CB1550; 61CB1743; 64HCA1860; 66ZC329; 78MI9). The product resulting from the condensation of one molar equivalent of *o*-phenylenediamine with C-1 and C-2 was fluorescent. This property has been used for their detection and determination. The product was found to exist in an equilibrium mixture of **211A** \rightleftharpoons **211B** \rightleftharpoons **211C** and not **212** (86MI9) (Scheme 46). The presence of two closely related isomers was indicated by ¹H-NMR spectroscopy, which showed the presence of two doublets due to H-2 and two singlets for each aromatic proton in **211B** (86MI9). Its ¹³C-NMR spectrum ruled out structure **212**, since it showed a single resonance for C-3 in the anomeric region instead of the two



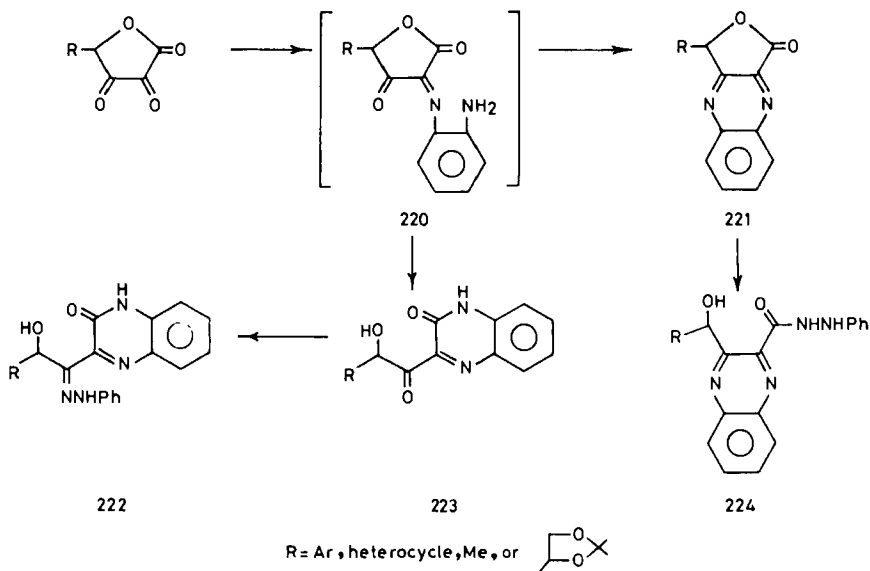
SCHEME 45

signals actually appearing in that region (101.6 and 105.0 ppm). The latter resonance was assigned to **211C** which has a similar C-3 configuration to that of **DH1**, which showed it at 104.8 ppm. Thus, the reactions can start by forming intermediate **209**, which has two chances for cyclization with either C-3 to give **210** or C-1 to give **212** or **211**. The latter was the preferred pathway for **DHA** and its analogues that have the C-3 masked in a



SCHEME 46

hemiacetal linkage and consequently decrease its reactivity in the cyclization step. On the other hand, the C-3 of the aryl analogue or of DHA that has a protected side chain, as in **16**, is more reactive. Consequently **221** is formed in addition to **223** via the intermediate **220** (Scheme 47). Although they could not be isolated, they could be trapped as their arylhydrazine derivatives **222** and **224**.



SCHEME 47

The reaction of **211** with arylhydrazines was claimed to have the structure **214** in its hydrated form (59CB1550). This structure was based on the formation of a diacetate. However, the acetate was found by X-ray and spectroscopic analyses to be the corresponding tri-*O*-acetate [90JCS(P1)2513]. The structure has also been revised to the acyclic form **213**, based on spectroscopic studies (mass and IR spectra) and periodate oxidation (78MI5, 78MI7, 78MI8). Its spectra indicated its existence as a mixture of isomers. The syn and anti isomers were given for **222**, which were derived from the methyl analogue (85MI3). Alternatively, the tautomeric equilibria between the hydrazone and the azo structures may be initiated by the transfer of a proton from the hydrazone residue to the nitrogen of the heterocyclic ring.

Periodate oxidation of **213** afforded the corresponding aldehydes **216**, whose reduction gave **219** (78MI2). During the oxidation of the corresponding semicarbazone, a product was isolated whose structure was formulated as the dimethylacetal **217** (81MI6).

Methylation (78MI2) of **213** with dimethylsulfate in alkaline solution afforded the *N*-methyl derivative **215**, whose structure has the acyclic form. Attachment of the methyl group to the nitrogen rather than the oxygen atom was proved by IR spectroscopy, which showed a band corresponding to the OCN group, and by ¹H-NMR spectra, which showed

a peak corresponding to the *N*-methyl group. No methyl groups were introduced on the hydroxyalkyl side chain, which was attributed to the immediate precipitation of the *N*-methyl derivative as soon as it was formed (78MI3). Periodate oxidation of **215** afforded **218**, which is the *N*-methyl derivative of **216**. Reduction of both **216** and **218** afforded the corresponding alcohols **219**, whose acetylation afforded the respective acetates.

1. *Imidazolyl Quinoxalinones*

This type of compound (**226**) was prepared by the reaction of the dianilinoethane with aldehyde **216** (78MI2).

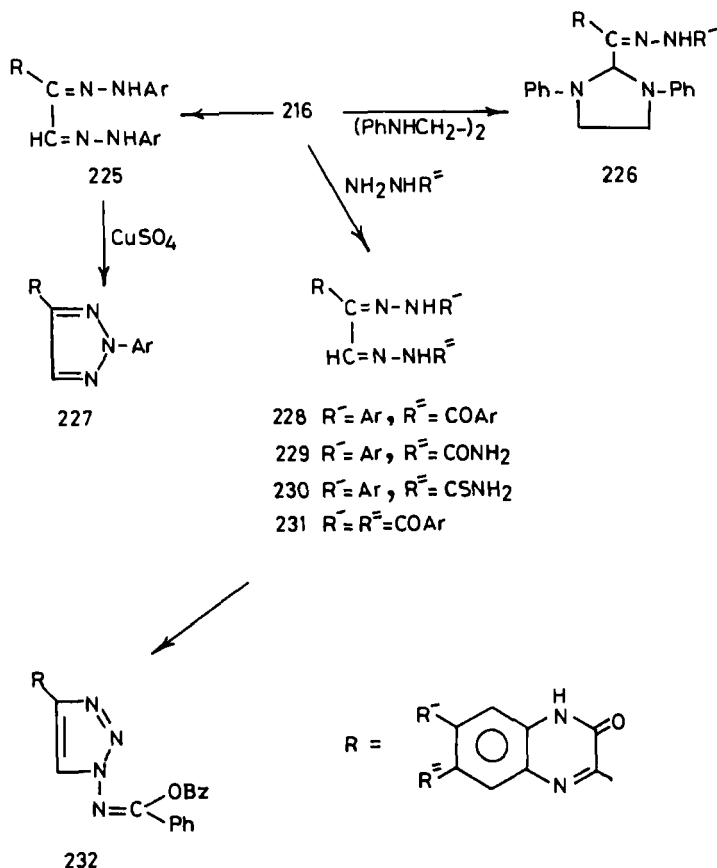
2. *Triazolyl Quinoxalinones*

This type of compound was prepared from aldehydes **216** by conversion into the bis(arylhydrazone) **225**, which, upon reaction with copper sulfate, afforded the corresponding triazoles **227** (Scheme 48). When **216** was allowed to react with amines or hydrazines having substituents that differ from that in **216**, the corresponding mixed bis(hydrazones) **228–230** were prepared. Attempted oxidation of bis(benzoylhydrazone) **231** with iodine and mercuric oxide to give **232** was investigated (80MI7).

3. *Pyridazinonyl Quinoxalinones*

Reaction of **216** with ethoxycarbonylmethylidene triphenylphosphorane gave **233**, which was successfully cyclized to **238** (81MI2; 87H2101) (Scheme 49). This reaction is a general method for synthesizing pyridazinones. The stereochemical outcome of the reaction of **216** with the phosphorane was found to afford the trans isomer **233**, as anticipated from a Wittig reaction. Inspection of models indicated this isomer could not be cyclized. Its cyclization could be achieved experimentally as a consequence of the thermal preisomerization of **233** into the cis isomer **236**, which led to its facile cyclization to **238**.

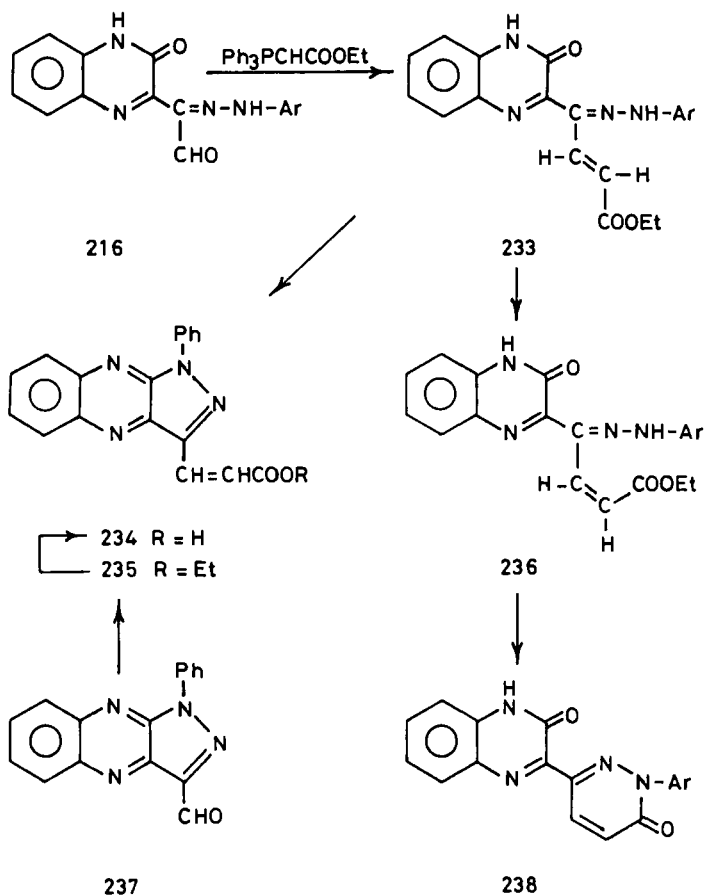
Attempted cyclization of **233** with alkali afforded **234** in addition to **238**, resulting from the elimination of one molecule of water from the hydrazone residue and the quinoxalinone ring and simultaneous hydrolysis of the ester group. This indicated the presence of two competitive reactions under conditions of cyclization. The structure of **234** was proved by its preparation by hydrolysis of **235**. The latter was prepared by the reaction of aldehyde **237** with the phosphorane. The structures were confirmed by studying their ¹H-NMR and mass spectra.



SCHEME 48

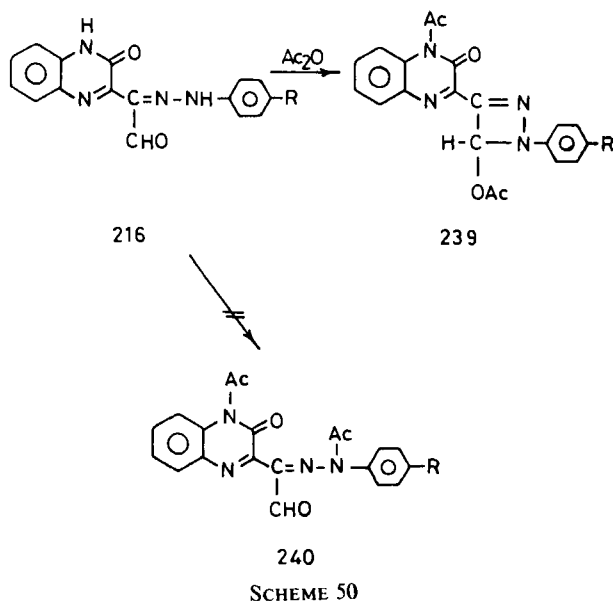
4. Diazetyl Quinoxalinones

Few reports are described (45RTC112; 47ACS54) regarding the diazete ring system. When aldehyde **216** reacted with acetic anhydride in pyridine, it did not afford any of the anticipated acetyl derivatives, such as **240**, but the structure of the product may be deduced as a 1,2-diazete-3-yl-1*H*-quinoxalin-2-one **239a** or a furoquinoxalin **239b** (unpublished results) (Scheme 50). The IR spectrum showed bands at 1615, 1635, 1705, and 1775 cm^{-1} . The ^1H -NMR spectrum of **239** showed two singlets at 1.99 and 2.76 ppm, due to the two acetyl groups. The singlet at 6.12 ppm is due to the CH attached to two heteroatoms. The aldehydic



SCHEME 49

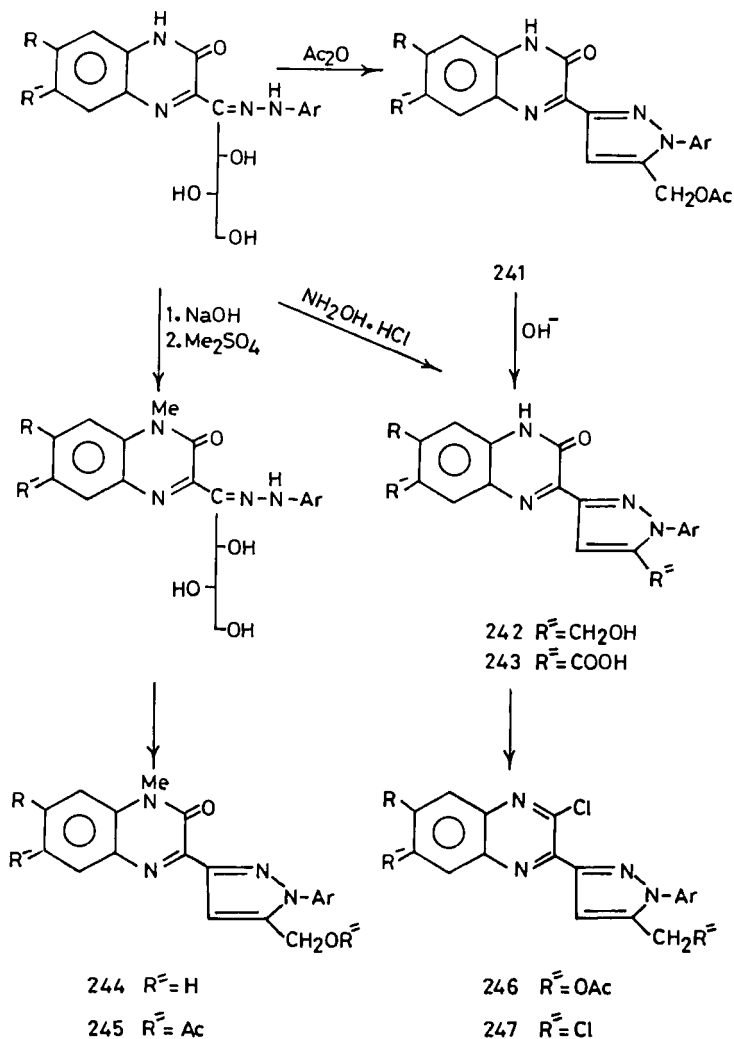
proton (anticipated at 9.6 ppm) as well as the 2 NH signals (at 11.23 and 12.63 ppm) of its precursor **216** disappeared in the spectrum of **239**. Its ^{13}C -NMR spectrum showed resonances at 20.65 and 22.38 ppm (due to the carbons of the two methyl groups) in addition to the two signals in the downfield region of the spectrum at 160.21 and 167.67 ppm (due to the two carbonyl groups). These data confirmed the presence of the two acetyl groups. The resonance at 89.69 ppm confirmed the presence of a carbon attached to two heteroatoms. In addition, the spectrum showed the presence of four resonances due to the six carbons of the phenyl group at 128.12, 128.46 (2C), 129.83 (2C), and 129.89 ppm. The spectrum also



showed resonances at 138.27, 141.17, and 141.54 ppm (due to the 2 C=N and CO), whereas the resonances at 127.86, 128.05, 128.27, 130.06, 130.89, and 131.38 ppm were due to the fused benzene ring.

5. *Pyrazolyl Quinoxalinones*

The glycerol portions in molecules **213** and **215** were found to be easily dehydrated with simultaneous ring-closure with the hydrazone residue, under the action of an acid catalyst to give pyrazoles **242** and **244**, respectively (59CB1550; 78MI1; 86G721; 88MI6; 89MI1; 89MI6) (Scheme 51). When the reagent was acetic anhydride, a simultaneous acetylation also occurred to give the corresponding acetylated derivatives **241** and **245**, respectively. Acetylation of **242** gave **241**, and deacetylation of **241** gave **242**, indicating their similarity in the basic skeleton of the heterocyclic ring. This dehydrative cyclization was found to be general for such compounds. Thus, compounds having various combinations of substituents on the quinoxalinone ring or the pyrazole ring can be prepared. Methylation of **242** gave **244**, and its oxidation with potassium permanganate gave the carboxylic acid **243**. The IR spectra of the products showed an amide band. The ¹H-NMR spectra of the acetylated derivatives **241** and **245**

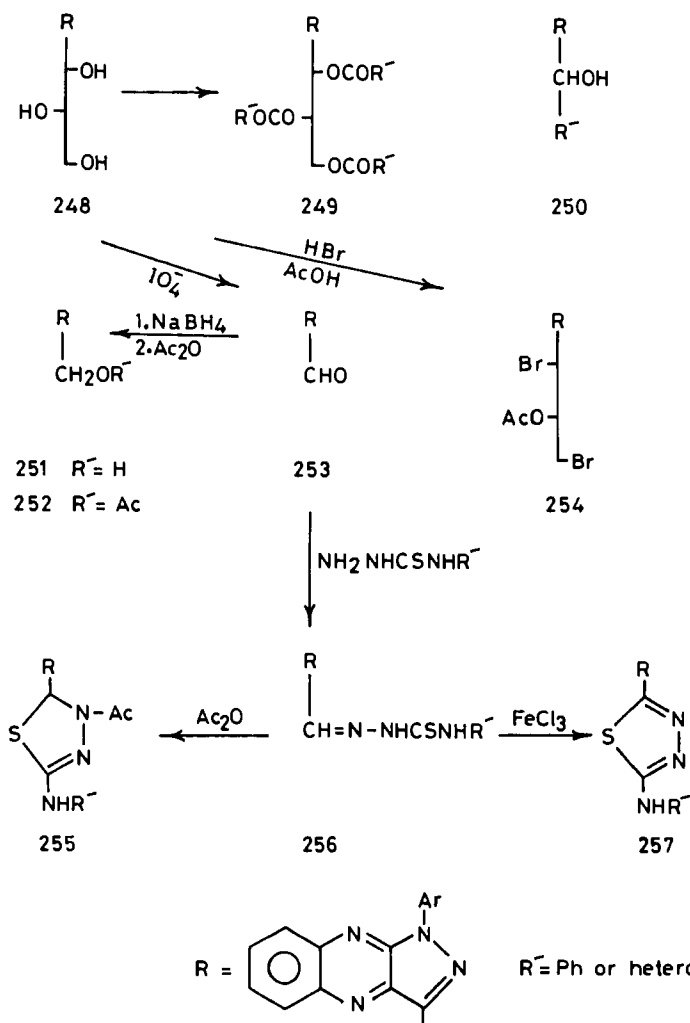


SCHEME 51

showed signals for one acetyl group and singlets for one methylene group, indicating the absence of a carbon-bearing proton adjacent to it. Moreover, one N—H signal appeared in **241–243**, whereas one N—Me signal appeared in the case of the methylated derivatives. Their mass spectra were also studied. Reaction of **241** and **242** with POCl_3 in DMF gave **246** and **247**, respectively.

6. Pyrazoloquinoxalines (Flavazoles)

The formation of 1-arylflavazoles from reducing sugars not substituted on O-2 and O-3 is a general reaction (41CB279, 41CB398; 84JOC2204). The reaction proceeds through the formation of an arylhydrazone group on C-3 of a sugar moiety attached to a quinoxaline ring. This prerequisite intermediate in flavazole synthesis could be generally formulated as **124**,



SCHEME 52

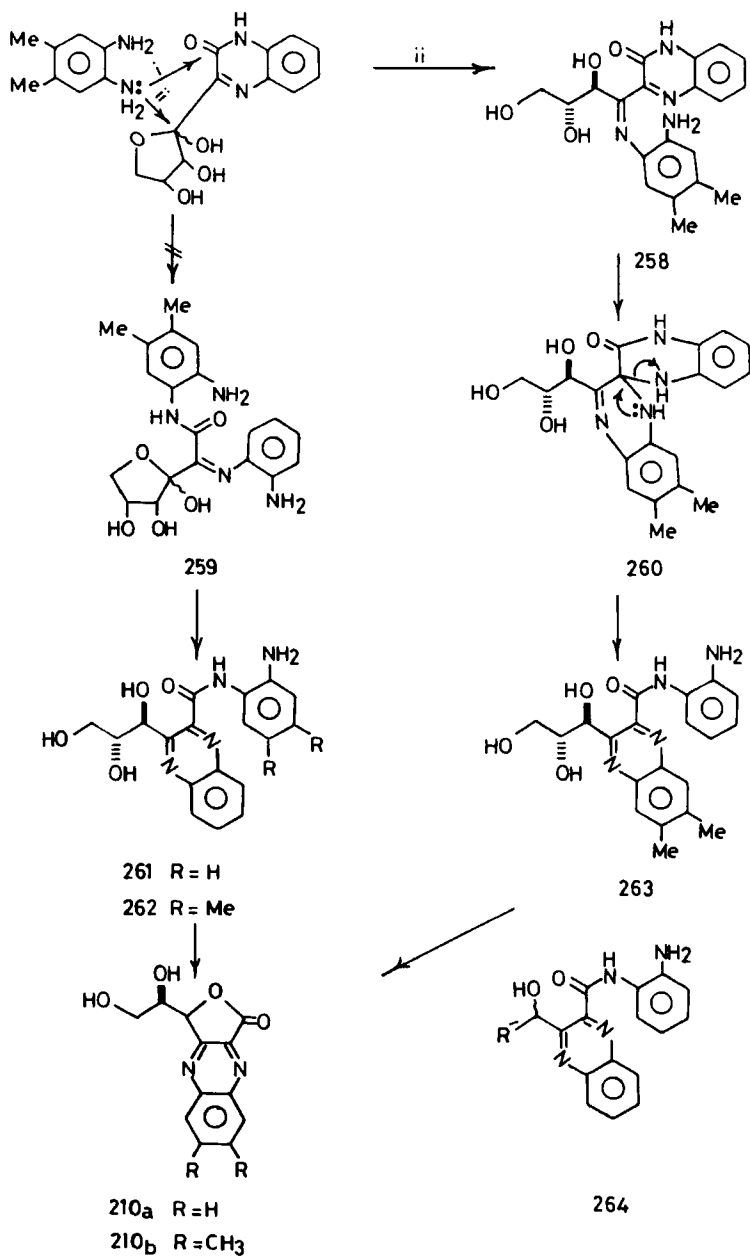
which, on treatment with alkali, gave the 1-arylflavazole **248**. The rearrangement of **124** proceeds in one hour in boiling dilute aqueous sodium hydroxide, but fission of the polyhydroxyalkyl side chain occurs in more concentrated alkaline solution. On the other hand, dissolution of **124** in alkali, followed immediately by acidification, regenerates the starting material. Formation of flavazoles from **3** via **124** provides an inexpensive and simple route to flavazoles otherwise obtained from L-galactose or L-talose. Various derivatives with groups on the aromatic rings as well as other isomers of the hydroalkyl residues were prepared (78MI1; 86MI4; 89MI5). Acylation of flavazoles afforded the corresponding tri-*O*-acylated derivatives **249**, whose conformations were studied (90MI3) (Scheme 52). Reaction of **248** with hydrogen bromide in acetic acid afforded the dibromoacetate **254**. Acetalation of **248** gave the corresponding acetals (89MI2, 89MI3, 89MI4). Periodate oxidation of **248** gave the aldehyde **253**, whose reduction followed by acetylation gave **251** and **252**, respectively. Reaction of **253** with thiosemicarbazide gave **256**, which could be transformed into the thiadiazoles and thiadiazolines **257** and **255**, respectively. The corresponding oxadiazoles and oxadiazolines were also prepared from the aroylhydrazones of **253** (90MI1).

The phenyl and heterocyclic analogues of ascorbic acid gave **222**, which, upon similar treatment with alkali, formed **250** (80MI6).

The mass spectral data of the flavazoles indicate the presence of the usual series of ions arising by elimination processes involving the sugar moiety attached to the flavazole ring. The principal fragmentation is rupture of the C-1—C-2 bond of the sugar moiety, giving the group of ions corresponding to $B + 29$, $B + 30$, and $B + 31$ (B is the heterocyclic ring). These ions frequently appear in the mass spectra of nucleosides. Complete loss of the sugar moiety gives rise to B , BH and $B + 2$ ions.

G. QUINOXALINES

Compounds such as **261**, **263**, and **264** can be prepared by the reaction of two molar equivalents of an *o*-diamine with DHA or its analogues (Scheme 53). Alternatively, they can also be obtained by the reaction of one molar equivalent with **210**. The structure of the product was found to be **263**, whatever the substituent on the C-5 of the furantrione ring. The amino group of **263** could be selectively acetylated, and acid hydrolysis gave the lactone **210** (64HCA1860; 66HCA2426), as confirmed spectroscopically (85MI1; 86MI9). Note that other structures having Schiff base-like derivatives or tricyclic rings had been proposed in the early investigations on such condensation products (34CB555, 34CB1750; 52AK369).



SCHEME 53

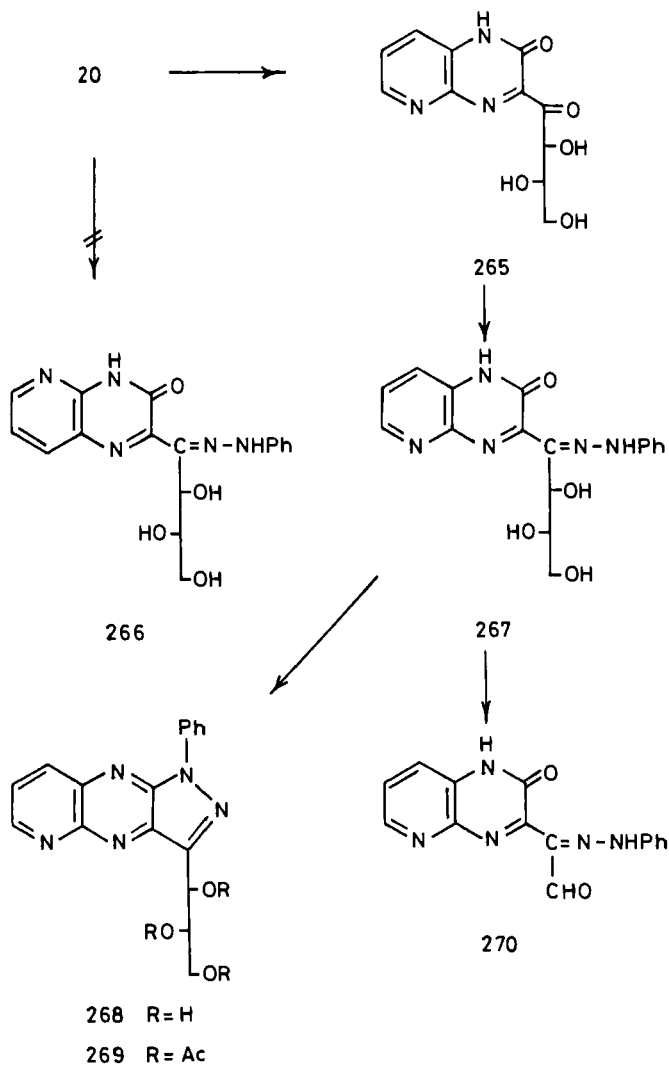
Compounds with various substituents on the aromatic ring and other analogues also have been prepared (77JHC927; 84MI2).

The reaction of the oxidized form of halogenodeoxyascorbic acids with *o*-phenylenediamine gave products formulated as Schiff base derivatives (80HCA1728). However, such structures should be reinvestigated. In a recent study, a possible reaction pathway was deduced by a sequential reaction of two different *o*-diamines with the *D-erythro* analogue of DHA. The mechanism of reaction of the first molecule to give **211a** was discussed in Section V,F. The reaction of the second molecule of diamine with **211a** most probably takes place through path ii by nucleophilic attack of the amino group on the anomeric carbon atom to give **258**, rather than by attack on the amide group to give **259**. Transformation of **258** to **263** can be effected by the attack of the second amino group on the C=N of the quinoxalinone ring to give the spiro intermediate **260**, whose rearrangement gave **263**. Alternatively, the first step may be the attack of the amino group on the C=N of **211a** to give **263** as well. A similar mechanism can be proposed for the reaction of DHA with *o*-diamines. However, the corresponding reaction with derivatives of DHA or its phenyl or methyl analogues may follow another mechanism because of the difference in the structure of the parent compounds, particularly in the first step, where the reactivity of C-3 may compete with C-1.

Polarographic studies on the reaction of DHA with phenylene diamine (61BCJ518; 67MI4; 83BCJ2033). showed, in acidic buffers, three cathodic DC-waves ($E_{1/2} = -0.240, -0.412$ and -0.634V vs. SCE, at PH 3.6), which differs appreciably from the behavior of the other dehydroreductones with the diamine. The polarographic behavior of each product from the reaction of DHA with the diamine was compared to that of the three waves, and the reaction mechanism was discussed.

H. PYRIDO[2,3-*b*]PYRAZINES

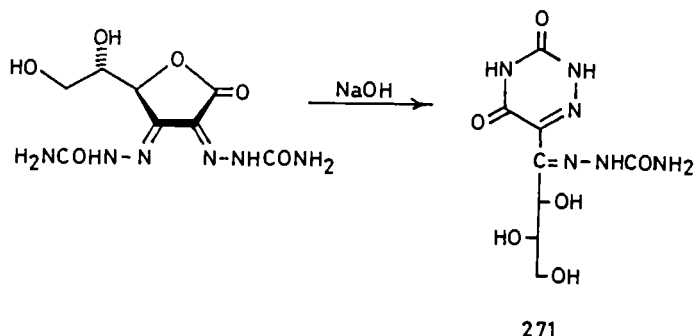
These compounds were prepared by the reaction of DHA with 2,3-diaminopyridine to give an intermediate, presumably a result of reaction on the C-1 and C-2 carbonyls, trapped as its phenylhydrazone **267** (Scheme 54). The structural assignment of the product as **267** and not **266** was based on considerations of the relative reactivities of the two amino groups of the diamine and the carbonyl groups of DHA. Periodate oxidation of **267** gave **270**. Reaction of **267** with alkali gave the pyrazolo-azaquinoxaline **268**, whose acetylation gave the corresponding acetate **269** (unpublished results).



SCHEME 54

I. 1,2,4-TRIAZINES

Treatment of bis(semicarbazone) **67** with dilute sodium hydroxide afforded the sodium salt of *L-threo*-2,3-hexodiulosonic acid 2,3-bis(semicarbazone), which, upon heating, afforded **271** (66BSF522) (Scheme 55).



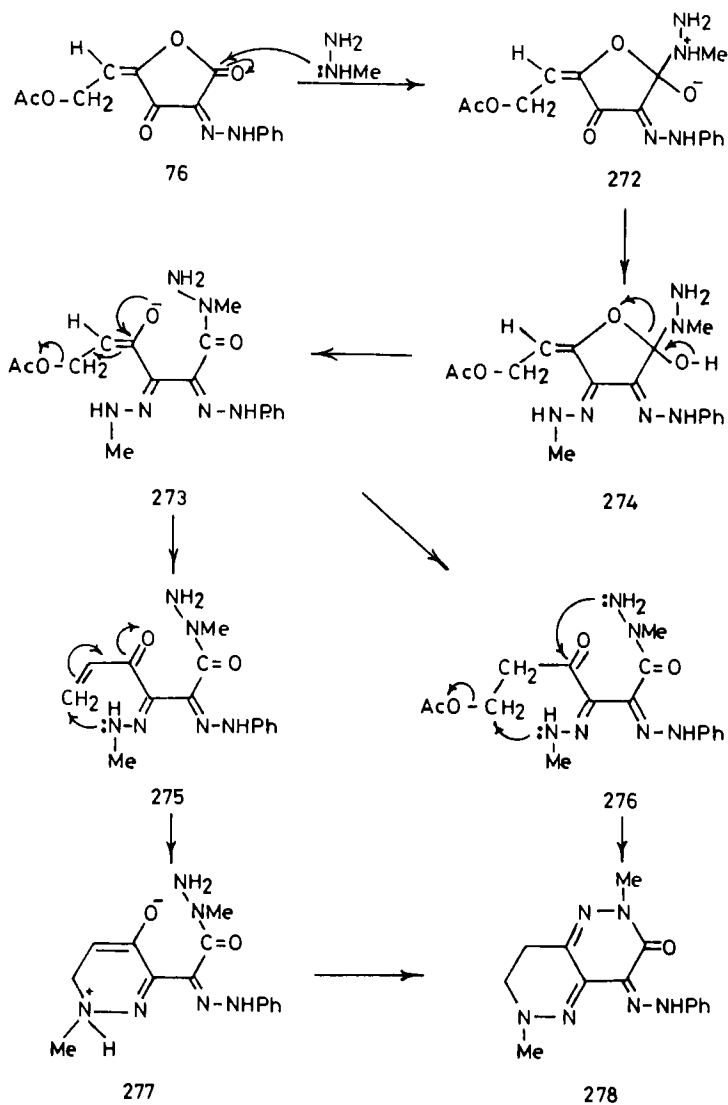
SCHEME 55

J. PYRIDAZINO[4,3-*c*]PYRIDAZINES

Acetylation of the monoarylhydrazones **60** gave the olefinic acetates **76**. When **76** was allowed to react with methylhydrazine, the product was not the anticipated mixed bis-hydrazone. A more complicated reaction occurred which lead to a bicyclic compound, resulting from the consumption of two moles of the methylhydrazine [76CI(L)372, 76MI3; 77MI1, 77MI4; 78MI6; 80JHC617]. Its IR spectrum showed the presence of a carbonyl amide band at 1640 cm^{-1} , whereas the lactone and the acetyl bands of its precursor had disappeared. The $^1\text{H-NMR}$ spectrum showed the presence of two adjacent methylene groups as two triplets at 2.73 and 3.30 ppm, two methyl groups at 3.15 and 3.48 ppm, and an NH at 13.56 ppm. Its mass spectrum showed a molecular ion peak at m/z 284.

These data agreed with either structure 2,6-dimethyl-3,4-dioxo-2,3,4,6,7,8-hexahydropyridazino[4,3-*c*]pyridazine-4-(arylhydrazone) **278** or 1-methyl-3-(1-methylpyrazoline-3-yl)-4,5-pyrazole-dione-4-(arylhydrazone). The latter was originally proposed for the product based on the assumption that a rapid rearrangement of the mixed bishydrazone, induced by the basic nature of the hydrazine into the corresponding pyrazoledione, took place. The latter was then cyclized on reaction with another molecule of the hydrazine. However, X-ray crystallography of the corresponding *p*-bromophenyl derivative showed that the structure was **278** (80JHC617) (Scheme 56).

Recently, a mechanism for the reaction was proposed based on the results of a study employing a quantum chemical calculation of the olefinic acetate **76** (90MI2). Thus, nucleophilic attack of hydrazine on **76** may occur at its various electrophilic centers. The electronic densities at these centers, decrease in the order $\text{C-5} > \text{C-4} > \text{C-3} > \text{C-1}$. These data indi-



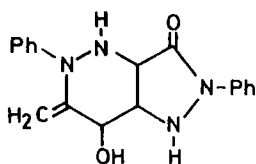
SCHEME 56

cate that C-1 should be the most electrophilic center in **76**. Consequently, the attack of methylhydrazine on **76** may occur on the lactone carbonyl rather than on the C-3 carbonyl. Scheme 56 shows the suggested mechanism. Thus, N-1 of the methylhydrazine attacks the carbonyl lactone to

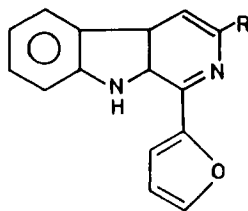
give **272**. A proton shift and ring opening may give **273** via **274**. A second molecule of the methylhydrazine may then react with the C-3 carbonyl. Two alternative cyclizations seem feasible. Intermediate **273** tautomerizes and accepts a proton to give **276**, which undergoes two types of cyclizations, whereby water and acetic acid molecules are eliminated to give **278**. Alternatively, elimination of acetate anion from **273** gives the unsaturated ketone **275** that cyclizes via a conjugate addition to give **277**, which further cyclizes to **278**.

K. PERHYDROPYRAZOLOPYRIDAZINES

Another type of pyridazine derivative was obtained by the reduction of a bis-hydrazone with lithium aluminium hydride. The structure of product **279** was tentatively assigned on the basis of spectral and chemical methods [72JOC(22)3523].

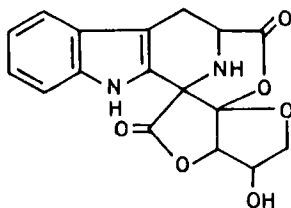


279

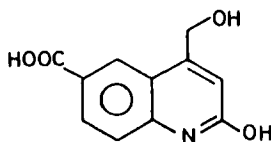


280 R = H

281 R = COOH



282

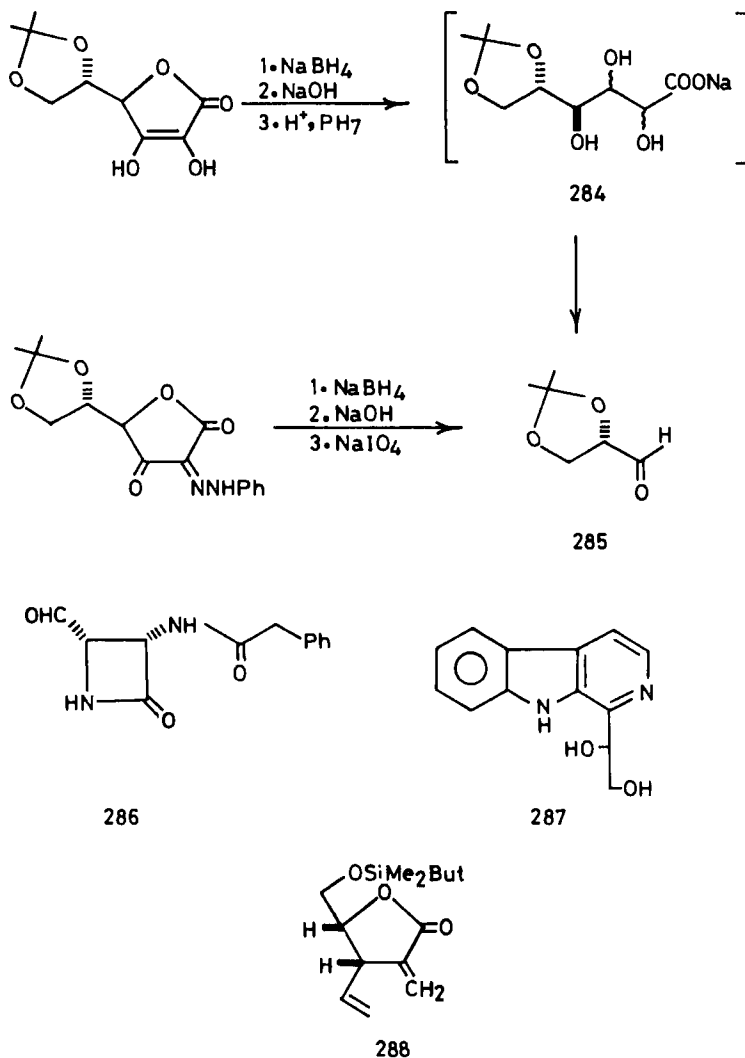


283

SCHEME 57

L. PYRIDO[3,4-*b*]INDOLE

The reaction between **3** and L-tryptophan in phosphate buffer gave several products, two of which were determined to be 1-(2-furyl)-pyrido[3,4-*b*]indole **280** and 1-(2-furyl)-pyrido[3,4-*b*]indole-3-carboxylic acid **281** (80CPB3143) (Scheme 57). Independently, several substances with



SCHEME 58

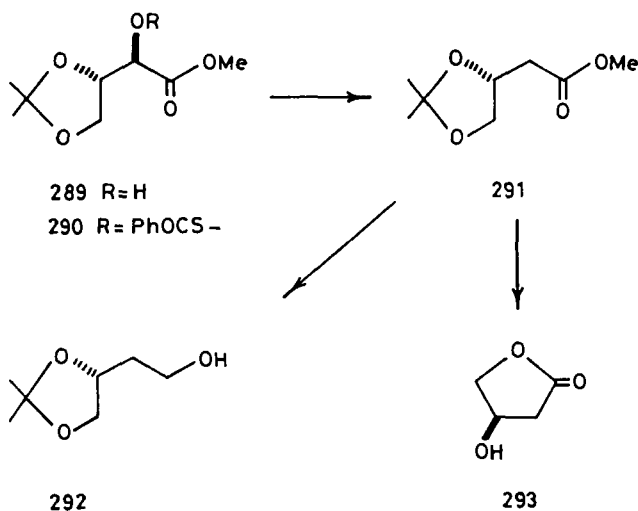
antioxidant activity were isolated from the mixture of DHA and tryptophan in ethanol. One of the main antioxidants was obtained in crystalline form from an *n*-butanol extract of the reaction mixture. Its structure was proposed to be a condensate of DHA with tryptophan, as in **282** (82ABC1199, 82ABC1207).

M. QUINOLINE DERIVATIVES

When DHA was allowed to react with *p*-amino-benzoic acid and hydrochloric acid, 6-carboxy-2-hydroxy-4-hydroxymethylquinoline (**283**) was obtained (64AK121).

N. L-GLYCERALDEHYDE AND THE SYNTHESIS OF NATURAL PRODUCTS

L-Ascorbic acid was used as a precursor for chiral building blocks via its convenient transformation to (*S*)-2,3-*O*-isopropylidenglyceraldehyde **285** (80JA6304; 82H327; 86T447) (Scheme 58). Thus, the acetonide in a multi-step, one-pot procedure was treated with sodium borohydride, which presumably reduces the ene-diol, followed by cleavage of the borate ester and the lactone ring with excess sodium hydroxide. This was fol-



SCHEME 59

lowed by careful neutralization, probably to give **284**, which without isolation was treated with lead tetraacetate to finally give **285**. Alternatively, the readily available acetonide **81** was transformed to **285** by reduction, hydrolysis, and cleavage with periodate. Glyceraldehyde **285** is a versatile chiron that can be transformed into various types of natural products and biologically important molecules such as **286–288**.

L-Threonate **289** obtained from **3** was converted to thiocarbonate **290**, which, on deoxygenation with $\text{Bu}_3\text{SnH/AIBN}$, gave dihydroxybutanoate **291** (Scheme 59). Treatment of **291** with aqueous H_2SO_4 in tetrahydrofuran gave lactone **293**, while reduction of **291** with LiAlH_4 gave butanetriol **292** (88S226).

ACKNOWLEDGMENT

The authors wish to thank Professor Z. M. El-Shafei for his valuable discussions.

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